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Prospective clinical trial to evaluate safety and feasibility of using a single port flexible robotic system for transoral head and neck surgery

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ABSTRACT

Introduction: The aim of this study was to determine the clinical safety and feasibility of a novel single-port flexible robot for Transoral Robotic Surgery (TORS).

Materials and methods: This was a prospective phase II / IDEAL stage 2 clinical trial of both benign and malignant lesions of the head and neck. The primary endpoint included conversion rates and perioperative complications within 30 days following surgery. The study was registered on www.ClinicalTrials.gov (NCT03010813). The Fisher's exact test and Mann-Whitney *U* test were used to compare categorical, and non-parametric data for the trial. A p value < 0.05 was considered to be statistically significant. Statistical analysis was performed with SPSS 20.0 (IBM Corp., Armonk, New York)

Results: Twenty-one patients safely underwent TORS with the da Vinci SP (Intuitive Surgical Inc., Sunnyvale, CA) demonstrating the feasibility of access to the nasopharynx, oropharynx, larynx and hypopharynx. There were no conversions of the robotic surgical system. There were no serious adverse events or adverse events related to the use of the robot at 30-day follow-up for all patients.

Conclusions: In a prospective Phase II clinical trial, a novel single-port flexible robotic system appears safe and feasible to use for transoral endoscopic head and neck surgery to access the nasopharynx, oropharynx, larynx and hypopharynx.

Introduction

The first-generation of rigid robotic surgical systems (Intuitive Surgical Inc., Sunnyvale, CA) was US Food and Drug Administration (FDA) approved for use in T1-2 tumors of the oropharynx and, since, been used with low surgical morbidity and mortality. However, the original system had certain constraints including the rigid, straight orientation and size of instruments, the inability to use all four instruments at once and the challenge in docking the patient side cart. To address these issues a novel, flexible, single-arm robotic surgical system (da Vinci SP Surgical system, Model SP999; Intuitive Surgical Inc.) was developed and first evaluated clinically in 2010 on 19 patients undergoing urological surgery in a prospective clinical trial [1].

Further technical refinements have been developed in this robotic system that have been described in pre-clinical applications for transoral robotic surgery (TORS) [2–4]. In brief, this next generation system within a 2.5 cm circular cannula houses a stereoscopic binocular camera and three 6 mm instruments, these instruments incorporate a snake like appearance similar to the 5 mm multiport Endowrist instruments combined with an additional elbow joint giving these instruments their flexibility. With adequate exposure, the flexible robotic arms allow the instruments to be deployed through the oral cavity to reach the nasopharynx, oropharynx, hypopharynx and larynx. Here we describe the results of the first clinical trial into the feasibility and safety of this updated novel flexible single-arm robot in transoral endoscopic head and neck surgery.

Materials and methods

Study design

This was a prospective institutional review board approved Phase II

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Table 1
Inclusion and exclusion criteria for the study.

Inclusion Criteria
- Age > 18 years
- Body mass index < 35 kg/m^2
- Suitable for minimally invasive surgery
- Willingness to participate as demonstrated by giving informed consent
- Adequate exposure to the surgical site according to the surgeon's judgment to proceed with surgery
- Locally recurrent T1/2 nasopharyngeal carcinoma
- T1/T2 oropharyngeal carcinoma
- Posterior 1/3 of tongue T1/2 oral cavity carcinoma that would otherwise require pull through or mandibulotomy
- Snoring/mild/moderate/severe obstructive sleep apnea (OSA), with lingual tonsil hypertrophy and/or epiglottic retroflexion, which significantly contributes to OSA as noted on sleep endoscopy; benign oropharyngeal lesions
- Primary supraglottic T1/2 carcinoma with N0/1/2a nodal disease after staging; primary glottic T1a/1b/2 carcinoma with N0/1/2a nodal disease after staging; recurrent laryngeal T1/2/3 carcinoma; benign laryngeal pathologies
- Irreversible bilateral vocal cord palsy
- T1/2 lateral wall and/or posterior pharyngeal wall hypopharyngeal carcinoma with N0/1/2a nodal disease after staging; any hypopharyngeal dysplasia
- Isolated retropharyngeal lymph node involvement with head and neck carcinoma

Exclusion Criteria
- Contraindication to general anesthesia
- Severe concomitant illness that drastically shortens life expectancy or increases risk of therapeutic intervention
- Untreated active infection
- Noncorrectable coagulopathy
- Presence of another malignancy or distant metastasis
- Emergency surgery
- Vulnerable population (e.g. mentally disabled, pregnancy)
- Severe Trismus
- Pregnant or suspect pregnant
- Involvement/abutment of the internal carotid artery; recurrent T3 or T4 lesions
- T3/4 oropharyngeal carcinoma; involvement of the carotid artery
- T3/4 oral cavity carcinoma; the need for free flap reconstruction
- No oropharyngeal component to OSA on sleep endoscopy
- Baseline aspiration on clinical examination; poor exercise tolerance, primary T3/4 supraglottic/glottic carcinoma; recurrent T4 laryngeal carcinoma
- Reversible bilateral vocal cord palsy
- T3/4 hypopharyngeal carcinoma; N2b or above neck disease; involvement of the pyriform apex; extensive involvement of the medial wall of the pyriform sinus
- Multilevel nodal involvement; multiple retropharyngeal lymph nodes involved; involvement of the carotid artery; involvement of the prevertebral fascia

clinical trial, classified as a Stage 2 surgical evaluation based on the Innovation, Development, Exploration, Assessment, Long-term Study (IDEAL) framework [5]. The study was conducted in accordance with the Declaration of Helsinki under the institutional review board and local regulatory body approval of The Chinese University of Hong Kong and was registered on www.ClinicalTrials.gov (NCT03010813).

Study population

Written informed consent was obtained from all patients. Both benign and malignant lesions of the head and neck were included with the inclusion and exclusion criteria listed in Table 1.

Surgical procedure

All surgical procedures were performed by surgeons JC, EW or RT on the trial following two sessions of two days of training on the system with cadavers at Intuitive Surgical Inc. All transoral robotic surgery was performed under general anesthesia with a two- team approach. The surgeon was located at the console with an assistant at the head of the patient to assist with suction and hemostasis. All sites were accessed through the oral cavity with the mouth retracted with either a Dingman, Boyle Davis, or Feyh-Kastenbauer (FK-WO) retractor. The tongue was retracted with a silk suture as needed while protecting the lower dentition with a piece of duoderm. Following this the 2.5-cm robotic port was placed 10–15 cm from the mouth opening and the instruments arms and cameras were deployed through the oral cavity and oropharynx. Lesions of the oropharynx, nasopharynx, larynx, or hypopharynx were approached, examined and/or resected.

Study endpoints

The primary endpoints included conversion rates and the incidence of perioperative complications within 30 days. The definition of a conversion for this study is an emergent change in the treatment plan to conventional minimally invasive surgery or to open surgery.

Perioperative complications including intraoperative complications and all complications occurring during the hospital stay or within 30 days after discharge were graded according to the Clavien-Dindo classification [6]. Complications of Clavien-Dindo grade III (those requiring surgical, endoscopic, or radiologic intervention) or above were regarded as major complications.

Secondary endpoints consisted of other key perioperative surgical outcomes including operative time, estimated blood loss, pain scores on a visual analog scale length of hospital stay, swallowing function based off the MD Anderson Dysphagia Inventory (MDADI) [7] and resection margins.

Statistical analysis

The chi-squared test (or Fisher's exact test when appropriate), Student's *t*-test, and Mann-Whitney *U* test were used to compare categorical, parametric, and non-parametric data, respectively. Longitudinal changes in mean quality of life were analyzed by the repeated measures analysis of variance test with post hoc pairwise comparisons using Bonferroni correction. A 2-sided P value < 0.05 were considered to be statistically significant. Statistical analysis was performed with SPSS 20.0 (IBM Corp., Armonk, New York)

Results

Twenty-one patients were enrolled in the trial with no conversions to alternative robotic systems nor other surgical approaches (transoral laser microsurgery or "open" surgery). The majority of patients were male, of Chinese ethnicity, ex-smokers with a median age of 60 years old as shown in Table 2. The pathology was malignant in eight cases and benign in thirteen cases, the specific diagnoses are shown in Table 3. The majority of cases were transoral resections in the oropharynx. For patients with human papilloma virus (HPV) -associated oropharyngeal squamous cell carcinoma (SCC), five arose from the tonsil and underwent lateral oropharyngectomy [8] (two T1 and three T2) (Fig. 1), one patient had an unknown primary and underwent a unilateral tongue base resection. In addition, one patient with an HPV positive tonsil primary underwent a retropharyngeal lymph node excision simultaneously. The HPV negative SCC (T1 lesion) arose in a patient with previous irradiation for nasopharyngeal carcinoma. In the two patients with laryngeal SCC, one underwent an examination under anaesthesia of the lesion (Fig. 2) and was the first case in this clinical series. The second patient with a primary laryngeal SCC underwent a transoral partial laryngectomy resection with a tracheostomy, the resection was achieved with clear margins (Fig. 3). Finally for the lesions of the nasopharynx and hypopharynx local excisions were performed. For the nasopharynx, the lesion was located in the central nasopharynx and resected as a local excision of a mass in the nasopharynx approached as previously described by Tsang et al. [3]. Similarly, the lesion in the hypopharynx was resected with a cuff of mucosa to perform a complete excision of the papilloma.

For exposure, the Crowe-Davis retractor was used in seventeen patients, the FK-WO retractor in three patients and the Dingman retractor in one patient. The mean docking time was 7 min (range 3–29 min), mean operative time was 61.1 min (range 35–215 min), mean estimated blood loss was 39.2 ml (range 5–100 ml), and mean length of stay was

Table 2
Demographics of the study population.

Variable	N (%)
Age	
Median (Range)	60 (41–75)
Gender	
Male	15 (71.4)
Female	6 (28.6)
Ethnicity	
Chinese	19 (90.4)
Caucasian	1 (4.8)
Indian	1 (4.8)
Smoking	
Current	5 (23.8)
Ex-smoker	10 (47.6)
Never	6 (28.6)
Alcohol	
Yes	3 (14.3)
No	18 (85.7)
Subsite	
Nasopharynx	1
Oropharynx	15
Larynx	4
Hypopharynx	2
Complications by Clavien Dindo Grade	
I	5
II	1
IIIa	2

Table 3
Pathology of specimens listed by site and subsite. SCC = squamous cell carcinoma.

Site	Subsite	Pathology	N%	Margins
Oropharynx				
	Tonsil	HPV positive SCC	5	Negative
	Tongue base	HPV positive SCC	1	Negative
		HPV negative SCC	1	Negative
		OSA	3	
		Asymmetric lingual tonsil	2	
		Papilloma	2	
		Ulcerated mucosa	1	
Nasopharynx				
		Lymphoid tissue	1	
Hypophyarnx				
	Neopharynx	Neopharyngeal stricture	1	
	Posterior Pharyngeal wall	Papilloma	1	
Larynx	Supraglottis	Fibrosis and lymphocytic infiltrate	1	
		SCC	2	Negative

10.4 days (range 1–30 days). Pain and swallowing functional outcomes of the patients with an oropharyngeal squamous cell carcinoma primary are shown in Table 4.

There were surgical complications in eight patients unrelated to the robot use. Case 4 who had previous radiotherapy and poor dentition pre-operatively had a fractured right lower molar that required a dental consultation. Case 5 had a 1 cm laceration of the tongue from the FK-WO retractor, case 7 had a temporary change in taste, case 8 was noted to have a small vocal cord haematoma at 30 day follow-up from intubation and case 18 had bleeding from granulation tissue at the site where silk sutures were used to retract the tongue that resolved by itself on follow-up visits without medical intervention. Case 11 had a drug allergy that resolved with medication. Case 15 had mild post radical tonsillectomy bleeding that was controlled at the bedside. There were no conversions or serious adverse events during the clinical trial.

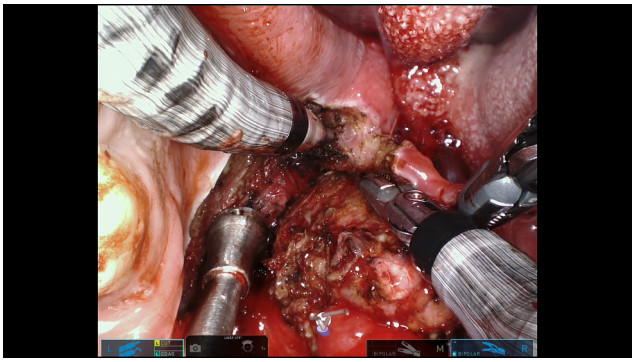

Fig. 1. A left radical tonsillectomy showing the use of three instrument arms. The fenestrated bipolar is retracting the resected to the right of the picture to straighten out folds at the tongue base to assist in the assessment of margins and oncological resections at the junction between the tonsil and tongue base. Monopolar cautery and Maryland bipolar were also used.

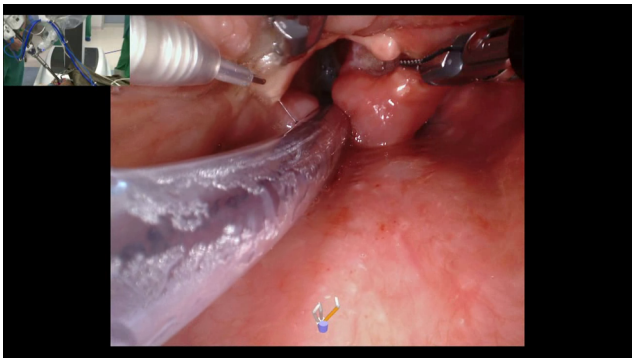

Fig. 2. Examination under anaesthesia of a patient with a recurrent T2 supraglottic squamous cell carcinoma with the endotracheal tube in place and retraction with a Crowe-Davis Oral Retractor. The left side instruments is a monopolar spatula. The midline instrument is a fenestrated bipolar used to retract the epiglottis while the Maryland bipolar touches the tumor.

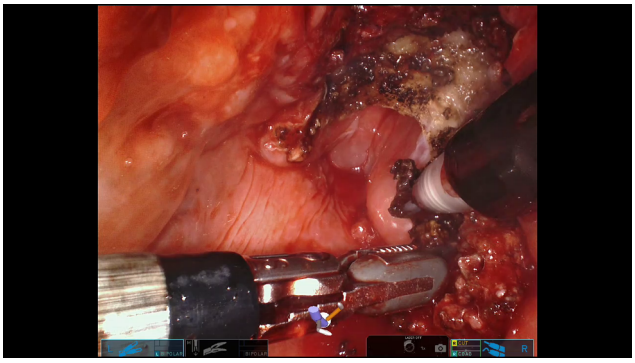

Fig. 3. Supraglottic partial laryngectomy in a patient with a T2 partial laryngectomy with a prophylactic tracheostomy. Two instruments arms were used for part of the resection as shown here with a Maryland Bipolar and monopolar spatula.

Discussion

As part of the multispecialty clinical trial the results of this safety and feasibility trial of the da Vinci SP (Intuitive Surgical Inc., Sunnyvale, CA) demonstrates that the device is likely safe and that it is feasible in performing transoral surgery to access the nasopharynx,

Table 4
Functional outcome scores preoperatively and at 2 weeks and 30 days postoperatively for patients that had an oropharyngeal squamous cell carcinoma primary resected. Pain was analysed using a visual analogue scale. MDADI = MD Anderson Dysphagia Inventory.

	Preoperative	2 weeks	30 days
Pain	0.4 ± 0.8	3.9 ± 3.1 (p = 0.03)	1.6 ± 1.8 (p = 0.23)
MDADI Global	77.11 ± 33.5	62.9 ± 35.5 (p = 0.18)	71.4 ± 30.2 (p = 0.78)
MDADI Physical	89.3 ± 15.5	62.9 ± 21.3 (p = 0.02)	64.6 ± 11.6 (p = 0.006)
MDADI Functional	91.4 ± 18.0	73.7 ± 16.6 (p = 0.01)	79.4 ± 16.1 (p = 0.02)
MDADI Emotional	89.6 ± 17.3	72.3 ± 17.9 (p = 0.01)	77.7 ± 15.4 (p = 0.03)

oropharynx, larynx and hypopharyngeal region for the treatment of both benign and malignant lesions. Importantly, this has been achieved in a predominantly Southern Chinese population utilizing a Crowe-Davis oral retractor to overcome the particular, smaller cranio-facial measurements in our population as compared to Caucasians [9].

TORS utilizing the da Vinci Si and Xi systems has been largely described for surgery of the oropharynx [10–13]. On a smaller scale TORS has also been described and shown to be feasible for surgery of the larynx, nasopharynx, hypopharynx and parapharyngeal space [14–16]. In this trial we had seven patients with oropharyngeal SCC, of which 6 had HPV positive SCC. All of these patients had negative margins following resection. Postoperative pain was significantly worse at 2 weeks as compared to preoperatively but returned towards baseline by 30 days postop as measured by the visual analog scale. The swallowing outcomes of this cohort of patients with the emotional, physical and functional MDADI scores were significantly worse at 2 weeks and 30 days postoperatively, with a trend towards improving swallowing function at 30 days compared to 2 weeks. These functional outcomes are similar to other studies evaluating swallowing function following TORS for oropharyngeal carcinoma [17–20].

Beyond the oropharynx we also able to evaluate the robotic system in a partial laryngectomy for squamous cell carcinoma in one patient. The use of TORS in potentially performing supraglottic laryngectomy was first described by Weinstein et al. in 2005 in canine model [21]. Subsequently, the use of TORS in performing both partial laryngectomies has been described in the literature, predominantly involving the supraglottis and utilizing rigid robotic systems [22–24]. However, TORS in addressing diseases of the larynx has been hampered by exposure, a lack of instrumentation and the rigid robotic arms [25]. Advancements in robotic systems have reignited the interest in the treatment of disease of the larynx as previously shown with the Flex® robotic system recently [26]. Here utilizing a flexible robotic system we were able to perform an oncological resection of a T2 suprgalottic carcinoma using a Crowe- Davis for retraction. In addition to the case with a carcinoma, we performed a partial laryngectomy using the same retractor on a patient with a lesion suspicious for carcinoma without a diagnosis despite multiple biopsies. Both these cases highlight the benefit that flexible robotic arms offer over the traditional rigid robotic arms.

There are some limitations with the current system, despite the benefit with the extra arm there is less working space for an assistant to, in particular, aid with suction. However, this can be largely overcome with a suction catheter placed through the nasal cavity into the desired location. Another limitation is the lack of bone instrumentation to resect, in particular tumours of the nasopharynx and skull base. Finally, tailor made instrumentation for finer dissections are needed to expand the performance for the system to be used on the glottic larynx.

In conclusion, the da Vinci SP robotic system appears safe and feasible for use in transoral endoscopic head and neck surgery and may offer great potential to advance the repertoire of minimally invasive surgery (MIS). Increased flexibility, improved visualization and maneuverability of the system allowed for MIS of the entire upper aerodigestive tract.

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Declaration of Competing Interest

Jason Y.K. Chan, Eddy W.Y. Wong, Raymond K. Tsang and Simon S.M. Ng received travel grants from Intuitive Surgical, Inc for training on the robotic system. Jason Y.K. Chan and Simon S.M. Ng are proctors for robotic training with Intuitive Surgical Inc.

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