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Minimally invasive surgery in the treatment of gastrointestinal and endocrine tumors

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Preface

Minimally invasive surgery (laparoscopic, robotic, transanal) has evolved and expanded considerably, especially in the last 30 years. It is important to point out that the potential advantages of a minimally invasive approach go beyond smaller incision size. Reduced interference with body homeostasis has positive impacts both in the clinical (less systemic inflammatory response to surgery, less complications, shorter hospital stay) and social spheres (less work and social inactivity, less disability, less fear and anxiety). In some ways, geriatric, obese, and otherwise vulnerable patients may experience a greater reduction in morbidity that their younger, healthier counterparts.

In this thesis, I focused on the minimally invasive approach in rectal cancer surgery and on the minimally invasive, transoral approach in thyroid surgery.

Part 1.

Does robotic proctectomy for rectal cancer increase the width of the circumferential resection margin?

A case-matched comparison by the same surgeon.

Abstract

Aim The literature has shown that robotic proctectomy for rectal cancer (RC) may result in wider circumferential resection margins (CRM) when compared to its open and laparoscopic counterpart. The aim of the study was to revisit this evidence, particularly in high-risk patients. The secondary aim was to compare 30-day outcomes in the three groups.

Methods The first 60 unselected consecutive patients with RC undergoing robotic proctectomy by one surgeon were prospectively collected during 3 years. Patients undergoing open or laparoscopic proctectomy were matched for gender, body mass index (BMI), and tumor distance from the anal verge. Pathologists were blind to surgical access.

Results Demographics data, tumor characteristics and the rate of neoadjuvant therapy did not differ in the three groups. Type of resection (low anterior or abdominoperineal) and the rate of stoma creation did not differ (p=1.00 and p=0.974). The rate of conversion to open was significantly lower in the robotic group when compared to the laparoscopic (p=0.039). The risk of conversion was significantly lower in the robotic group for male gender (n=69; 9% vs 25%; OR 0.30; 95%CI 0.007–1.00; p= 0.043) and u-LAR (n=52; 11% vs 40%; OR 0.13; 95% CI 0.003–0.99; p=0.035). OR time was significantly longer in the robotic group

(<0.001). The time of resumption of solid diet, the length of hospital stay and the rate of complications were significantly lower in the minimally invasive groups (laparoscopic and robotic). A lower rate of patients in the robotic group experienced a LOS ≥ 6 days (p<0.001). TME quality (p=0.787), distal margin (0.790) and pTN stage (p=0.966) were comparable. The number of harvested nodes was significantly higher in the minimally invasive approaches (robotic or laparoscopic) (p= 0.001). After performing a DSCF test for multiple comparisons analysis the CRM resulted wider in the laparoscopic and robotic groups (p=0.020). However, the rate of positive CRM did not differ in the three groups (p=0.861 for CRM ≤ 1mm; p=0.236 for CRM ≤ 2 mm). The risk of CRM ≤ 2 mm was significantly higher in the laparoscopic group for male gender (n=69; 9% vs 27%; OR 0.14; 95% CI 0.003–0.98; p= 0.036) and obese patients (n=53; 10.7% vs 36%; OR 0.32; 95% CI 0.006–1.00; p= 0.040).

Conclusion The results of this study show two significant advantages of the robotic approach, especially in difficult patients and although the inclusion of the surgeon's learning curve.: lower rate of CRMs ≤ 2 mm in males and obese patients, lower conversion rates in male patients and in patients undergoing a u-LAR. More trials focused on high-risk patients are needed to clarify the effective benefits of the robotic approach on this subgroup of patients.

Introduction

New surgical technologies aim to overcome the challenge of the narrow pelvic space and technically demanding dissection typical of pelvic cancer surgery. Laparoscopic technique has been described as noninferior to open rectal cancer (RC) surgery for short term outcomes within European trials[1] and these findings were later supported by similar oncological outcomes in an American trial[2]. However, significant benefits of robotic RC surgery over laparoscopy have yet to be demonstrated [3]. The main limitations of robotic surgery have been identified to include increased costs and prolonged operating time[3]. Nevertheless, quality of data is a current limitation with the majority deriving from small cohorts[4]. A previous study found that Circumferential Resection Margins (CRMs) were significantly wider when a surgeon's learning curve in robotic proctectomy was compared to matched open and laparoscopic RC cases by the same surgeon[5]. In fact, robotic access with its wristed instruments may allow overcoming the laparoscopic trocars' fulcrum effect, which limits the range of movements in the confined space of the pelvis[6] and may allow to achieve wider CRM, a metric known as an independent predictor of cancer-specific survival at multivariate analysis[7].

The primary aim of this study was to revisit the evidence suggesting that the width of CRMs may be increased by robotic proctectomy as compared to the open and laparoscopic counterpart performed by the same surgeon in unselected consecutive patients with RC and to perform a subgroup analysis for high risk patients (males, obese, patients undergoing ultralow resections, neoadjuvated patients). The secondary aims were to compare 30-day outcomes in the three groups.

Methods

The first 60 unselected consecutive patients with RC undergoing robotic proctectomy by one surgeon at a single institution were prospectively collected during a 3-year period. Patients undergoing open and laparoscopic proctectomy were matched for gender, body mass index (BMI) and tumor distance from anal verge with a range of ± 0.05 at the propensity score. Data were retrospectively analyzed from the prospectively maintained database of the Unit of Digestive Surgery, Careggi University Hospital, Florence. Inclusion criteria were elective, curative-intent surgery for rectal adenocarcinoma performed by one surgeon at one institution. Exclusion criteria were stage IV or recurrent disease and emergency surgery. RC was defined as adenocarcinoma located within 12 cm from anal verge. The primary study endpoint was the width of the CRMs evaluated according to Quirke et al [8]. Pathologists were blinded to surgical access. The American Society of Anesthesiology classification [9] was used in the preoperative assessment although it does not predict the risk for a particular patient. The Colorectal Physiological and Operative Severity Score for evaluation of Morbidity and mortality (CR-POSSUM) instead was used to estimate the risk of morbidity and mortality of each patient[10]. BMI was defined as weight (in kg) divided by the square of the height (in m). Obesity was defined as a BMI ≥ 30. The American Joint Commission on Cancer (7th edition) staging scheme for rectal carcinoma was used for the pathological staging of the tumor[11]. Anastomotic leak was defined according to the classification proposed by the International Study Group of RC and assessed for patients undergoing restorative surgery[12]. Postoperative ileus was defined as postoperative prolonged (> 3 days) nil per os or need of nasogastric tube insertion. Ultralow anterior resection (u-LAR) was defined as a TME with anastomosis ≤ 5 cm from the anal verge. Conversion to open surgery was defined as an abdominal incision to continue the procedure under direct visualization before full mobilization of the rectum. Complications were analyzed according to the Clavien-Dindo [13] classification. In > 90% of laparoscopic and robotic cases an enhanced recovery program was applied.

Statistical analysis

An automated matching procedure in the SAS ® software (version 8.2; SAS Institute, Inc., Cary, North Carolina, USA) randomly selected patients operated by laparotomy and laparoscopy from a pool of potential comparators who fulfilled the matching criteria.

Continuous variables were reported as mean (standard deviation) or median (interquartile range); categorical variables as frequencies and percentage. Significant differences between the two groups were tested by Pearson X^2 for categorical variables or the nonparametric Kruskal-Wallis test for continuous variables. The Dwass-Steel-Critchlow-Fligner (DSCF) test was used for multiple comparison analysis between groups.

All tests were two-sided and $p < 0.05$ was considered statistically significant. Subgroups analyses were conducted to estimate the odds ratios (ORs) for conversion to laparotomy and CRM involvement between groups. ORs and their 95% confidence intervals (95% CI) were estimated using a univariate logistic regression model.

Statistical analysis was performed using IBM SPSS Statistic Version 25.0 (IBM corp., Armonk, NY).

Results

Matched patients in the 3 groups were comparable for age (p=0.605), gender (p=0.789), BMI (p=0.407), ASA class (p=0.869), POSSUM scores (p=0.683), preexisting comorbidities (p=0.498) and previous abdominal surgery (p=0.587) (Table 1). Tumor distance from anal verge (p=0.912), tumor location (p=0.976), preoperative stage (p=668) and neoadjuvant chemoradiation (p=0.517) were similar in the 3 groups. (Table 2). OR time was longer in the robotic group (p<0.0001). The rate of conversion to open was higher in the laparoscopic group (p=0.039). There was no difference in stoma creation (p=0.974) and type of resection (p=1.000) (Table 3). The mean postoperative day of resumption of solid diet (p<0.001) and length of hospital stay (LOS) (p<0.001) were lower in the robotic and laparoscopic groups. A lower rate of patients in the robotic group experienced a LOS ≥ 6 days (p<0.001). (Table 4). There were no deaths up to 30 days after surgery. The overall rate of complications was higher in the open group (p<0.001), this significance was determined by the rate of Superficial Site Infections (SSI) (p=0.001). Readmissions (p=0.561) and complications grade according to Clavien-Dindo classification (p=0.685) were comparable in the 3 groups (Table 4).

The quality of TME (p=0.787), distal margins (p=0.790) and postoperative TN stage (p=0.966) were comparable. The width of CRMs was significantly wider in robotic and laparoscopic patients (p=0.020). The number of nodes collected was significantly higher in the minimally invasive groups (p=0.001) (Table 5).

In the laparoscopic and robotic groups, a subgroup analysis to assess conversion rate and CRM ≤ 2 mm was performed for at-risk subgroups (male patients, patients undergoing ultralow anterior resection: u-LAR, obese patients). The risk of conversion was significantly higher in the laparoscopic group for male gender (n=69; 9% vs 25%; OR 0.30; 95%CI 0.007–1.00; p= 0.043) and u-LAR (n=52; 11% vs 40%; OR 0.13; 95% CI 0.003–0.99; p=0.035). The risk of CRM ≤ 2 mm was significantly higher in the laparoscopic group for male gender (n=69; 9% vs 27%; OR 0.14; 95% CI 0.003–0.98; p= 0.036) and obese patients (n=53; 10.7% vs 36%; OR 0.32; 95% CI 0.006–1.00; p= 0.040). (Table 6).

Discussion

The results of this study show two significant advantages of the robotic approach: lower rate of CRMs ≤ 2 mm in males and obese patients, lower conversion rates in male patients and in patients undergoing a u-LAR. These results underline the ability of the robot to perform low rectal dissection more easily, even in a difficult anatomic pelvis. On the other hand, we reported better results in terms of length of stay, complications, harvested nodes, CRM width in the minimally invasive (robotic and laparoscopic) vs the open approach. Operative time was significantly longer in the robotic approach, with a trend to shorten and to be comparable to that of the other two approaches during the surgeon's learning curve.

Differently from a previously published study[5], which reported wider CRMs in the robotic group over the laparoscopic and open approaches, in the present study CRMs resulted significantly wider in the minimally invasive groups over the open. Interestingly, robotic surgery resulted an independent factor for wider CRM in at-risk subgroups such as males and obese patients. The robotic approach to RC may help to perform an oncological good dissection thanks to its endo-wrist technology overcoming the fulcrum effect in the pelvis as previously reported by a consensus conference[6]. A study analyzing 400 consecutive laparoscopic and robotic TMEs did not report an association between approach and positive CRM in at-risk subgroups [14]. However, the impact of robotic proctectomy on CRM remains unclear as most authors report CRM as a discrete variable rather than as a continuous variable, in mm. Moreover, the definition of CRM involvement varies from greater than 1 mm[15,16] to greater than 2 mm[17]. This lack of standardization leads to controversial results with some authors reporting no significant differences in CRM involvement between the robotic and laparoscopic approach [15,16,18,19-21], whereas others reported significantly decreased CRM involvement after robotic proctectomy [5, 22]. In 2002, Nagtegaal et al reported that local recurrence and liver metastases rates were significantly decreased in 656 non-radiated patients at a median follow-up of 35 months, provided that the CRM was > 2 mm rather than < 2 mm[23]. The published study we aimed to revisit the evidence found that CRM was significantly wider when a surgeon's learning curve in robotic proctectomy was compared to matched open and laparoscopic cancer cases by the same surgeon (10.5 mm vs. 8 mm vs. 4 mm)[5]. Another study reported significantly wider CRM after robotic TME when compared to transanal Total Mesorectal Excision (TaTME) although there were not differences in the quality of TME, tumor size, tumor location and preoperative neoadjuvant therapy. Authors concluded that a potential explanation is the greater precision of the robotic approach[24]. Nonetheless, we still do not know the potential clinical significance of a CRM wider than 2 mm. A study reported a significant increasing trend in recurrence free survival after RC surgery when patients were divided according to CRM width: < 1 mm, 1.1 – 5 mm, > 5 mm[25] pointing at CRM as a predictor of cancer-specific survival[7]. More specific analysis on patients with at-risk features and a standardization in the definition of CRM positivity should be performed to shed a light on the effective advantage of the robotic approach on at-risk patients.

The robotic approach was associated with lower conversion rates and was an independent predictor in male patients and in patients undergoing u-LAR. This data is also reported two recent series[14,26] and by two meta-analysis[27,28], although results from the largest RCT available on robotic RC surgery failed to prove its superiority over laparoscopy[29].

Robotic surgery was associated with prolonged operative time in our series and this is consistent with previous evidence[30]. However, it should be underlined that the robotic group included operations performed during the surgeon's learning curve and that after the first 20 cases operating time had a tendence to shorten becoming comparable to the one of the open and laparoscopic approaches. Operating time has been the subject of several studies attempting at defining the optimal number of robotic proctectomies required to overcome the learning curve[5]. The literature seems to indicate that the required number of cases would range from 15 to 25 robotic proctectomies depending on the surgeons' previous experience in open rectal surgery as well as their laparoscopic skills[31-33].

Surgical innovations should follow a systematic pathway of validation [34]. To date, the decision to choose a robotic approach to RC is still controversial, often driven by surgeons' preference rather than evidence-based considerations. Safety and feasibility have been frequently reported but analysis of postoperative outcomes remains inconclusive [35,36]. Analysis of costs often refers to short time frames and this could mislead one to assume that higher operative costs of robotics are not balanced by favorable outcomes[37]. Although intraoperative outcomes are frequently in favor of robotic surgery [19,38], postoperative short-term outcomes are reported to be similar between the 2 approaches as reported also the present study where minimally invasive approaches were associated with shorten length of stay and complications. Interestingly, we reported a significantly lower rate of LOS $\geq$ 6 days in the robotic group. This could be due to the advantages of minimally invasive surgery itself and to the application of the enhanced recovery program in more than 90% of patients in both groups. Interestingly, a recent study[26] comparing 317 consecutive robotic and 283 consecutives laparoscopic proctectomies demonstrated improved short-term outcomes in terms of length of stay and complications in the robotic over the laparoscopic approach, even after logistic regression analysis.

The main limitations of this study are its retrospective and nonrandomized setting. The first 60 consecutive robotic proctectomies were matched with open and laparoscopic cases extracted from the surgeon's database. Therefore, there could be an inherent risk of selection bias and results must be interpreted accordingly. However, the matching, the consecutive inclusion of robotic patients and the highly standardized surgical approach for all the techniques may limit the risk of systematic error related to sample selection.

A strength of this study is that pathologists were blinded to surgical access and that one surgeon performed all the operations, in order to avoid biases.

In conclusion, our study underlines the benefits of robotic approach, especially for difficult patients, although the inclusion of the surgeon's learning curve. Surely, surgeon's experience plays a major role in the results of a technique. More trials focused on high-risk patients are needed to clarify the effective benefits of the robotic approach on this subgroup of patients. With this regard, a European prospective controlled trial (RESET: Rectal Surgical Evaluation Trial) has been proposed to evaluate open, laparoscopic, robotic, transanal TME for sphincter-sparing surgery for mid-low RC in high risk patients.

TABLES

Values expressed are mean ± standard deviation or as n (%) unless otherwise indicated.

Table 1: Demographics

	Open (n=60)	**Laparoscopic (n = 60)**	**Robotic (n = 60)**	**p value**
Age (years)	67.4 ± 11.4	69.5 ± 10.1	65.5 ± 11.3	0.605
Gender (%)				0.789
Male	38 (62.5)	36 (60)	33 (55)	
Female	22 (37.5)	24 (40)	27 (45)	
BMI (kg/m^2)	24 ± 3	26 ± 2.63	25 ± 3	0.407
ASA (%)				0.869
Class II	12 (20)	10 (25)	13 (22.5)	
Class III	48 (80)	30 (75)	47 (77.5)	
POSSUM				0.683
Physiology Score	10.7 ± 1.9	10.3 ± 2.1	9.5 ± 2.45	
Operative Severity Score	10.8 ± 0.6	11 ± 0.2	11.3 ± 0.87	
Mortality %	24% ± 0.9	26.% ± 1.3	21% ± 1.1	
Preexisting Comorbidities (%)				0.498
Cardiovascular	30 (50)	27 (45)	33 (55)	
Renal	1 (1.6)	3 (5)	1 (1.6)	
Endocrine	9 (15)	7 (11.6)	6 (10)	
GI	6 (10)	1 (1.6)	1 (1.6)	
Pulmonary	7 (11.6)	4 (6.6)	6 (10)	
Neurological	3 (5)	3 (5)	1 (1.6)	
Other	3 (5)	13 (21.6)	1 (18.3)	
Previous Abdominal Surgery (%)	30 (50)	36 (60)	36 (60)	0.587

Values are given as mean ± SD or *n* (%)

ASA, American Society of Anesthesiology; BMI, Body Mass Index.

Table 2: Tumor Characteristics

	Open (n=60)	**Laparoscopic (n=60)**	**Robotic (n=60)**	**p value**
Distance from Anal Verge (cm)	8.25 ± 4.64	8.45 ± 4.82	7.52 ± 5.36	0.912
Tumor location (%)				0.976
Posterior	15 (25)	15 (25)	15 (25)	
Anterior	18 (30)	18 (30)	18 (30)	
Lateral	9 (15)	6 (10)	9 (15)	
Circumferential	18 (30)	21 (35)	18 (30)	
Preoperative stage				0.668
I	15 (25)	18 (30)	12 (20)	
II	30 (55)	24 (40)	27 (45)	
III	15 (25)	18 (30)	21 (35)	
Neoadjuvant chemoradiation (%)	36 (60)	39 (65)	42 (70)	0.517

Values are given as mean ± SD or *n* (%)

Table 3: Intraoperative Data

	Open (n=60)	Laparoscopic (n=60)	Robotic (n=60)	p value
OR time (min)	240 ± 50.3	220.2 ± 54.6	315.7 ± 76.7	***<0.0001***
Ileostomy (%)	40 (67)	41 (68)	41 (67.5)	0.974
Type of Resection (%) Low Anterior Abdominoperineal	 54 (90) 6 (10)	 54 (90) 6 (10)	 54 (90) 6 (10)	1.000
Conversion to open	/	10 (16.6)	3 (5)	***0.039***

Values are given as mean ± SD or *n* (%)
OR: operating room

Table 4: Postoperative Data

	Open (n=60)	Laparoscopic (n=60)	Robotic (n=60)	p value
Solid Diet (POD)	5 (4-7)	2 (2-3)	2 (1-3)	***< 0.001****
Length of Stay (days)	11 (10-13)	4 (4-7)	3 (3-5)	***< 0.001****
Length of Stay ≥ 6 days	36 (60)	24 (40)	13 (23)	***< 0.001°***
Complications - Anemia - Ileus - Leak - SSI - Cardiopulmonary - Urinary	47 (78.3) 4 (6.6) 13 (21.6) 10 (16.6) 15 (25) 1 (1.6) 4 (6.6)	30 (50) 3 (5) 10 (16.6) 9 (15) 4 (6.6) 2 (3.3) 2 (3.3)	24 (40) 2 (3.3) 9 (15) 5 (8.3) 3 (5) 3 (8.3) 2 (3.3)	***< 0.001**** 0.704 0.610 0.364 ***0.001**** 0.596 0.592
Readmissions	10 (16.6)	8 (13.3)	6 (10)	0.561
30 days mortality	0	0	0	/
Clavien Dindo I II IIIa IIIb	 7 (14.8) 29 (61.7) 3 (6.5) 8 (17)	 4 (13.4) 14 (46.6) 6 (20) 6 (20)	 3 (12.7) 13 (54.1) 4 (16.6) 4 (16.6)	0.685

Values are given as median ± interquartile range or *n* (%)
POD, postoperative day.

- *Significant for robotic and laparoscopic vs open
- ° Significant for robotic vs laparoscopic and open

Table 5: Pathology Data

	Open (n=60)	Laparoscopic (n = 60)	Robotic (n = 60)	p value
TME Quality				0.787
Complete (%)	52 (86.6)	52 (86.6)	54 (90)	
Near complete (%)	3 (5.1)	5 (8.3)	5 (8.3)	
Incomplete (%)	5 (8.3)	3 (5.1)	1 (1.7)	
CRM (mm)	7.825 ± 6.305	8.925 ± 6.208	11.60 ± 5.36	***0.020****
Positive CRM				
- ≤ 1 mm	3 (5)	2 (4)	2 (4)	0.861
- ≤ 2 mm	14 (23.3)	10 (16.6)	7 (11.6)	0.236
Distal Margin (mm)	21.5 ± 15.12	21.5 ± 15.12	20.5 ± 16.46	0.790
Nodes Collected	13 (9-42)	18 (12-50)	18 (12-50)	***0.001****
pTpN Stage				0.966
Stage I (%)	27 (45)	30 (50)	28 (46.6)	
Stage II (%)	16 (26.7)	14 (23.3)	15 (25)	
Stage III (%)	17 (28.3)	16 (26.7)	17 (28.4)	

Values are given as mean ± SD or *n* (%) or median (range)

- *Significant for robotic and laparoscopic vs open
-

Table 6: Subgroup analyses: conversion rate and CRM ≤ 2 mm according to four subgroups (male patients, patients undergoing ultralow anterior resection, obese patients, neoadjuvated patients)

	R-TME	L-TME	Total	OR[a] (95%CI)	p
Conversion[b]					
Males	3/33 (9%)	9/36 (25%)	12/69(17.3%)	0.30(0.007–1.00)	**0.043**
u-LAR	3/27 (11%)	10/25 (40%)	13/52 (25%)	0.13(0.003–0.99)	**0.035**
Obese	2/28 (7.1%)	5/25 (20%)	7/53 (13.2%)	0.16 (0.3 –1.65)	0.101
Neoadjuvant	5/42 (11%)	5/39 (13%)	10/74 (13.5%)	1.56 (0.43–5.18)	0.603
CRM ≤ 2 mm					
Males	3/33 (9%)	10/36 (27%)	13/69 (18.8%)	0.14(0.003–0.98)	**0.036**
u-LAR	4/27 (14.8)	3/27(11.1%)	7/52 (13.4%)	1.52 (0.46–5.17)	0.593
Obese	3/28 (10.7)	9/25 (36%)	12/53 (22.6%)	0.32(0.006–1.00)	**0.040**
Neoadjuvant	3/42 (7%)	6/39 (16%)	9/74 (12%)	0.17 (0.4 –1.68)	0.106

u-LAR: ultralow anterior resection

[a] Odd ratios are given for R-TME with respect to L-TME

[b] Conversion rate: number of conversions/total number of patients in given subgroup

Part 2.

An easier option for "invisible scar" thyroidectomy: Hybrid-TransOral Endoscopic Thyroidectomy Submental Access (H-TOETSA). Experience on twenty-two consecutive patients.

Abstract

Background: Transoral endoscopic thyroidectomy vestibular approach (TOETVA) is currently the only "cervical invisible scar" procedure with a surgical access close to the thyroid area. The aim of this technical note was to describe a hybrid technique with a vestibular and a submental access as applied in 22 consecutive patients undergoing lobectomy.

Methods: Out of 502 thyroidectomies performed from February 1/2018 to May 31/2019 feasibility of Hybrid-TransOral Endoscopic Thyroidectomy Submental Access (H-TOETSA) was assessed in 22 patients meeting the inclusion criteria. Differently from TOETVA, a central trocar ($\leq$ 10 mm) for the camera was placed on the natural skin depression immediately under the chin. A left 3 mm and a right 5 mm (or 3 mm if a 3 mm energy device was available) trocars were placed in the vestibulum (as in TOETVA).

Results: operative time was 74,32 ($\pm$ 34,16) min. Two temporary recurrent nerve paralysis and three lip/chin dysesthesia were observed. In two patients an additional 3 cm horizontal access was performed 2 cm above the clavicle to control a persistent bleeding. Patients complained pain only in the first postoperative hours. All patients perceived excellent cosmetic results even at postoperative day 1.

Conclusions H-TOETSA was feasible and resulted to have some technical and clinical advantages maintaining the purpose to avoid a visible scar on the neck.

Introduction

Kocher's neck incision was performed for thyroidectomy until the end of the last century. Technological progress, indications for surgery at lower thyroid volumes and increasing attention to the aesthetic results led to the development of less invasive operations: shorter neck incisions (i.e. minimally invasive thyroidectomy – MIT – incision < 6 cm or minimally invasive video-assisted thyroidectomy – MIVAT – incision ≤ 2 cm) , reduced neck dissection, extra cervical approaches (i.e. robotic transaxillary). However, these supposed-to-be less invasive operations were not always minimally invasive nor they guaranteed the expected aesthetic results with high costs and long operative time. Additionally, as large or multiple surgical incisions were outside the neck, wide dissection was required to overcome the distance between the surgical access and the gland. These reasons, together with the diffusion of the endoscopic and robotic approaches, led to increasing operative time and costs.

The transoral endoscopic thyroidectomy vestibular approach (TOETVA) is the latest proposed operation and is currently the only "scarless" or more appropriately "hidden and invisible scar" technique. TOETVA follows all the steps of a conventional thyroidectomy having the advantage of a surgical access close to the thyroid area[1-2]. Additionally, the central trocar for the camera allows a good view of both the thyroid loggias. This technique does not require dedicated endoscopic or robotic instruments, which are expensive and not always available[3].

The aim of this technical note was to describe our experience on a hybrid procedure with a combined vestibular and submental access: H-TOETSA (Hybrid-TransOral Endoscopic Thyroidectomy Submental Access).

Hybrid TransOral Endoscopic Thyroidectomy Submental Access

TOETVA was introduced into our Unit in September 2017 with the standard technique as previously described by Wang[1] and later modified by Anuwong[2]. The main difficulty reported during our learning curve was the placement of the 10 mm central trocar requiring the detachment of the chin tissue from the mandibular periosteum: this maneuver resulted in postoperative painful hemorrhagic infarction and prolonged edema of the lower lip. The placement of the 2 lateral trocars was easier, but it also could cause ecchymosis, edema and lower lip dysesthesia. Furthermore, the conflict between the three trocars caused limitations in the movement of endoscopic instruments. A patient scheduled for TOETVA who already had a submental post-traumatic scar, prompted us to conceive some changes to the original procedure. The hybrid procedure seemed to be feasible and easily reproducible, with some advantages over TOETVA. For these reasons we began to perform it routinely. A central 10-12 mm trocar for the camera was placed on the previous scar or on the natural skin depression immediately under the chin (Fig 1). From this site a 5 mm endobag (Fannin UK Limited T/A –Espiner Medical-Clavedon,Somerset- UK) was also inserted for the specimen extraction. There are two reasons for using a 10-12 mm trocar: 1) an incision of at least 2 cm is always required for specimen extraction, 2) the 10-12 mm trocar helps in lifting the miocutaneous flap without causing ischemia and decubitus (as the 5 mm trocar would do exerting its pressure on a smaller surface). A left 3 mm trocar for 3 mm laparoscopic rigid instruments (Ab Medica s.a.s.-Mery Sur Cher-France) and a right 5 mm (or 3 mm) trocar for the energy device were placed in the standard vestibular positions. The 3 mm right vestibular trocar was placed when a 3 mm energy device was available (JustRight Surgical, Louisville, Colorado-USA) (Fig. 2)

Matherials and Methods

Out of 502 thyroidectomies performed from February 1, 2018 to May 31, 2019, 22 H-TOETSAs were performed at the Unit of Endocrine Surgery, Florence University Hospital. Patients' data were prospectively registered in the Unit database. Approval by the ethical committee and informed consent from all patients were obtained.

All patients underwent routine investigation including thyroid function test, neck ultrasonography and fine needle aspiration. We started our learning curve performing lobectomies with a double purpose: to become confident with the technique and to avoid longer operative times.

Inclusion criteria were the same as for TOETVA: benign thyroid nodules no more than 4 cm in size, low risk malignant nodules no more than 2 cm in size and goiters not exceeding 50 ml in volume. Additionally, a strong patient motivation in avoiding a visible cervical scar was mandatory. Exclusion criteria were thyroiditis or previous cervical interventions.

The Visual Analog Pain Scale (VAS) was assessed 6 hours after the intervention, at postoperative day (POD) 1 and POD 7. All the patients were preoperatively assessed for vocal cord function by flexible laryngoscope and postoperatively at days 7 and 30. Hypoparathyroidism was defined as a level of PTH and Ca lower than 1.3 pmol/l and 8.5 mg/dl respectively as measured at POD 1 and 30. The aesthetic result was evaluated at POD 1 and 30 using the Numerical Score System (NSS).

Results

Table 1 shows the results in details. All patients were female with a mean age of 38,1 (± 13.3) years. Mean time for patients/OR setup and mean operative times were 28 (± 2.5) min and 74,3 (± 34,16) min respectively. Mean thyroid volume was 31,2 ml (± 13,8) with a maximum nodule diameter of 35,14 (± 10,3) mm. Eighteen patients were affected by a single cytologically benign nodule and four by a suspect nodule. Seven patients had an hyperfunctioning goiter.

An additional 3 cm upper jugular incision was needed in two cases: 1) to stop the bleeding of a large nodule in an obese patient 2) to secure bleeding under visual control from the contralateral operative field in another patient. Two patients were discharged the same day of the operation and the others in the morning of POD 1. One patient suffered by surgical site infection. Two temporary recurrent nerve paralysis were observed, which resolved within 1 month. No permanent recurrent nerve paralysis or surgical site hematoma were reported. Permanent hypocalcemia was not registered as only lobectomies were performed. Three patients complained of lip/chin dysesthesia and one patient of mild lip-chin oedema on the site of the right 5 mm vestibular trocar, both resolved within 1 month. Patients complained of pain only in the first postoperative hours. All patients perceived excellent cosmetic results even at POD 1 with a mean value of NNS scale of 8,0 (± 0,8), confirmed at POD 30 .

Discussion

A poor correlation between scar length and the aesthetic result, mainly related to short incisions and the trauma due to excessive skin traction, is well known in thyroid surgery[4] suggesting that the highest patient satisfaction is reached by avoiding cervical scars.

We performed H-TOETSA only to the 4.3% of patients (22/502) as it requires the same strict selection criteria of TOETVA[5]. Additionally, an essential selection criteria is a strong motivation to avoid a cervical visible scar.

The safety and feasibility of the transoral approach (vestibular or submental) are strictly related to the surgeon's experience in laparoscopic and thyroid surgery[6-10]. Our initial experience with TOETVA confirmed its feasibility and reproducibility without any infectious or permanent nerve complications. However, it was associated with longer operative time when compared to conventional thyroidectomy or other minimally invasive approaches[3,11]. Preliminary data comparing 5 TOETVAs and 22 H-TOETSAs showed a significantly longer operative time in the first group (98.7 $\pm$ 21.7 min vs 74.3 $\pm$ 34.1 min; $p<0.05$) and an increased postoperative morbidity in terms of: temporary lip/chin dysesthesia (100% vs 13%; $p<0.05$), lip/chin hematoma (40% vs 0%; $p<0.05$), lip/chin oedema (100% vs 4.5%; $p<0.05$), seroma (20% vs 4.5%). However, our transoral experience began with performing the 5 TOETVAs which represent the first cases of our learning curve. Higher numbers and a structured prospective trial are needed to draw more solid conclusions in comparing these two techniques. TOETVA is challenging, particularly at the beginning of the learning curve, and has some intrinsic limitations. Additionally, the primary (if not the unique) aim of the transoral thyroidectomy is to avoid a visible scar on the neck and preserve the cosmesis. Hence, the transoral approach has not anymore to be intended and classified as a minimally invasive procedure, as suggested by a recent anatomo-hystological study on TOETVA by Celic et al. 2019 [12]. The idea of performing a hybrid approach was prompted by a young patient who already had a little post-traumatic scar under the chin. From the first case we perceived that the submental approach could simplify the procedure and maintain excellent aesthetic results. In fact, the submental incision is already widely used in plastic surgery for neck lift procedures with excellent cosmetic results. We noticed that even before complete wound remodeling, the scar is already invisible thanks to its position.

After these first 22 cases we found the following advantages in H-TOETSA:

- It decreases the distance between access and gland with less tissue dissection when compared to all the other extra-cervical techniques;
- It decreases technical problems due to the central trocar insertion across the mimetic muscles and neurovascular structures of the inferior lip;
- It increases the endo-oral space without the need of nasotracheal intubation, often traumatic and cause of nasal mucosal bleeding;
- It avoids the detachment, often very challenging, of the chin tissue from the mandibular periosteum;
- It decreases lower lip trauma and, consequently, potential lesions of the mental nerves (medial branches) with a lower incidence of postoperative dysesthesia;
- It eliminates the conflict between trocars thanks to better instrument triangulation;

- It prevents contact between the central trocar and the mandible with less potential trauma;
- It provides direct visual access to the platysma and allows easy creation of the subplatysmal space with hydrodissection and blunt instruments such as curved forceps and dilators of increasing diameter;
- It increases the degree of movement of the 2 lateral trocars in the working space thanks to the extra-oral position of the central trocar;
- It allows the insertion of the endobag directly through the central access (without the trocar) and an easier specimen extraction as it is not prevented by the fixed and inflexible chin. In fact, the submental incision is elastic and can be adapted to the specimen size, extending the indication to goiters of higher volumes.
- It achieves excellent aesthetic results. Particularly the use of two 3 mm vestibular trocars do not leave any sign at the end of the procedure.
- It decreases the potential risk of lower lip and surgical site infections thanks to the placement of the central trocar outside the mouth.

In the next cases we expect to achieve a decrease in postoperative complications, already rare in this first series. The aesthetic results, a primary endpoint in this intervention, were good even after 7 days from surgery. (Fig 3-4).

H-TOETSA has the same limitations as TOETVA: it is still limited to low glandular volumes, benign or low-risk malignant lesions and requires an experience in laparoscopic and thyroid surgery.

A common advantage of H-TOETSA and TOETVA is that they do not require dedicated endoscopic or robotic instruments, achieving excellent aesthetic results and not impacting on costs.

Future perspectives

A further implementation of this technique consists in the systematic adoption of a 3 mm vessel sealing energy device (JustRight Surgical, Louisville, Colorado-USA) and a 3 mm bipolar forceps (Gunter Bissinger Medizintechnik Gmbh, Teningen-Germany) allowing the placement of a 3 mm right vestibular trocar, further decreasing the trauma and improving the aesthetic result. A 3 mm camera (ConMed Corporation, New York-USA) may be interchangeable with all 3 trocars, making the intervention even easier adding at the same time a better lateral vision.

TABLE AND FIGURES

Values expressed are mean ± standard deviation or as n (%) unless otherwise indicated.

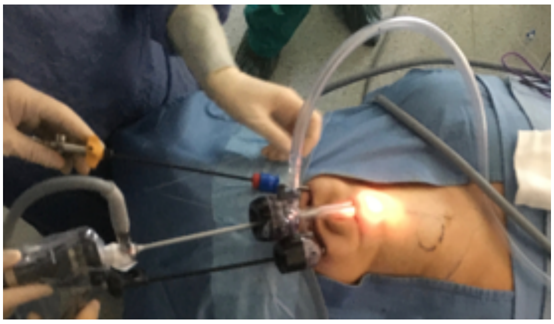
Table 1: patients characteristics

	H-TOETSA (n=22)
Age (years, mean ± SD)	38.18 ± 13.3
Gender (Female/Male)	22/0
OR and patient setup; min, mean (± SD)	28 (± 2.5)
Operative time; min , mean (± SD)	74,32 (± 34,16)
Mean volume; ml, mean (± SD)	31,27 (± 13,85)
Max nodule diameter; mm, mean (±SD)	35,14 (± 10,37)
Cytology	
- Benign nodule; n (%)	18 (81,8)
- Suspect nodule; n (%)	4 (18,2)
Hyperfunctioning goiter; n (%)	7 (31,8)
Additional neck incision; n (%)	2 (9,1)
Discharge on POD 0; n (%)	2 (9,1)
Discharge on POD 1; n (%)	20 (90,9)
Surgical site infection; n (%)	1 (4,5)
Temporary RLN paralysis; n (%)	2 (9,1)
Permanent RLN paralysis; n (%)	0(0)
Surgical site hematoma; n (%)	0(0)
Permanent hypocalcemia; n (%)	0(0)
Lip/chin oedema; n (%)	1(4,5)
Lip/chin hematoma; n (%)	0(0)
Lip/chin dhysaestesia; n (%)	3 (13,6)
Seroma; n (%)	1(4,5)
Postoperative pain (1-10)	
-6 hours; mean (± SD)	4.1 (± 0.2)
-POD 1; mean (± SD)	2.1 (± 0.1)
-POD 7 (mean ± SD)	1.0 (± 0.3)
Aesthetic result (NSS 1-10)	
POD 1; mean (± SD)	8,0 (± 0.8)
POD 30; mean (± SD)	8,9 (± 0.5)

OR=operating room; RLN= Recurrent laryngeal nerve; POD= postoperative day

Figure 1: central trocar placement

Figure 2: operative field at the end of trocars placements



Figures 3-4

References part 1

1. van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ; COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol. 2013 Mar;14(3):210-8.
2. Fleshman J, Branda ME, Sargent DJ, Boller AM, George VV, Abbas MA, Peters WR Jr, Maun DC, Chang GJ, Herline A, Fichera A, Mutch MG, Wexner SD, Whiteford MH, Marks J, Birnbaum E, Margolin DA, Larson DW, Marcello PW, Posner MC, Read TE, Monson JRT, Wren SM, Pisters PWT, Nelson H. Disease-free Survival and Local Recurrence for Laparoscopic Resection Compared With Open Resection of Stage II to III Rectal Cancer: Follow-up Results of the ACOSOG Z6051 Randomized Controlled Trial. Ann Surg. 2019 Apr;269(4):589-595. doi: 10.1097/SLA.0000000000003002. PMID: 30080730; PMCID: PMC6360134.
3. Staderini F, Foppa C, Minuzzo A, Badii B, Qirici E, Trallori G, Mallardi B, Lami G, Macrì G, Bonanomi A, Bagnoli S, Perigli G, Cianchi F. Robotic rectal surgery: state of the art. World J Gastrointest Oncol 2016; 8(11): 757-771.
4. Holmer C, Kreis ME. Systematic review of robotic low anterior resection for rectal cancer. Surg Endosc. 2018 Feb;32(2):569-581. doi: 10.1007/s00464-017-5978-y. Epub 2017 Dec 7. PMID: 29218670.
5. Barnajian M, Pettet D III, Kazi E, Foppa C, Bergamaschi R. Quality of total mesorectal excision and depth of circumferential resection margin in

rectal cancer: a case matched comparison of first 20 robotic cases. Colorectal Dis 2014; 16(8): 603-609.

6. Szold A, Bergamaschi R, Broeders I, Dankelman J, Forgione A, Lango T, Melzer A, Mintz Y, Conde SM, Rhodes M, Satava R, Tang CN, Villalonga R. European association of endoscopic surgeons (EAES) consensus statement on the use of robotics in general surgery. Surg Endosc 2015; 29(2): 253-288.
7. Nagtegaal ID, Quirke P. What is the role for the circumferential resection margin in modern treatment for rectal cancer? J Clin Oncol 2008; 26(2): 303-312.
8. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986; 2: 996-999.
9. Dripps RD, Lamont A, Eckenhoff JE. The role of anesthesia in surgical mortality. JAMA 1961; 178: 261-266.
10. Prytherch DR, Whiteley MS, Higgins B, Weaver PC, Prout WG, Powell SJ. POSSUM and Portsmouth POSSUM for predicting mortality. Br J Surg 1998; 85: 1217-1220.
11. Edge SB, Byrd RD, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual, 7th edition. New York: Springer, 2010.
12. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, Holm T, Wong WD, Tiret E, Moriya Y, Laurberg S, den Dulk M, van de Velde C, Büchler MW. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study

Group of Rectal Cancer. Surgery. 2010 Mar;147(3):339-51. doi: 10.1016/j.surg.2009.10.012. Epub 2009 Dec 11. PMID: 20004450.

13. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009 Aug;250(2):187-96. doi: 10.1097/SLA.0b013e3181b13ca2. PMID: 19638912.
14. Rouanet P, Bertrand MM, Jarlier M, Mourregot A, Traore D, Taoum C, de Forges H, Colombo PE. Robotic Versus Laparoscopic Total Mesorectal Excision for Sphincter-Saving Surgery: Results of a Single-Center Series of 400 Consecutive Patients and Perspectives. Ann Surg Oncol. 2018 Nov;25(12):3572-3579. doi: 10.1245/s10434-018-6738-5. Epub 2018 Aug 31. PMID: 30171509.
15. Bianchi PP, C C, Locatelli A, Spinoglio G, Zampino MG, Sonzogni A, Crosta C, Andreoni B. Robotic versus laparoscopic total mesorectal excision for rectal cancer: a comparative analysis of oncological safety and short-term outcomes. Surg Endosc 2010; 24(11): 2888-2894.
16. Park JS, C G, Lim KH, Jang YS, Jun SH. Robotic-assisted versus laparoscopic surgery for low rectal cancer: case-matched analysis of short term outcomes. Ann Surg Oncol 2010; 17(12): 3195-3202.
17. D'Annibale A, P G, Monsellato I, Pende V, Lucandri G, Mazzocchi P, Alfano G. Total mesorectal excision: a comparison of oncological and functional outcomes between robotic and laparoscopic surgery for rectal cancer. Surg Endosc 2013; 27(6): 1887-1895.

18. Baek SJ, KS, Cho JS, Shin JW, Kim J. Robotic versus conventional laparoscopic surgery for rectal cancer: a cost analysis from a single institute in Korea. World J Surg 2012; 36 (11): 2722-2729.
19. Trastulli S, F E, Cirocchi R, Cavaliere D, Avenia N, Scianmameo F, Gullà N, Noya G, Boselli C. Robotic resection compared with laparoscopic rectal resection for cancer: systematic review and meta-analysis of short term outcome. Colorectal Dis 2012; 14(4): e134-e156.
20. Memon S, H A, Murphy DG, Bressel M, Lynch AC. Robotic versus laparoscopic proctectomy for rectal cancer: a meta-analysis. Ann Surg Oncol 2012; 19(7): 2095-2101.
21. Saklani AP, L D, Hur H, Min BS, Baik SH, Lee KY, Kim NK. Robotic versus laparoscopic surgery for mid-low rectal cancer after neoadjuvant chemoradiation therapy: comparison of oncologic outcomes. Int J Colorectal Dis 2013; 28(12): 1689-1698.
22. Kang J, Y K, Min BS, Hur H, Baik SH, Kim NK, Lee KY. The impact of robotic surgery for mid and low rectal cancer: a case-matched analysis of a 3 arm comparison-open, laparoscopic, and robotic surgery. Ann Surg 2013; 257(1): 95-101.
23. Nagtegaal ID, Marijnen CA, Kranenbarg EK. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. Ann J Surg Pathol 2002; 26:350-357
24. Perez D, Melling N, Biebl M, Reeh M, Baukloh JK, Miro J, Polonski A, Izbicki JR, Pratschke J, Aigner F. Robotic low anterior resection versus transanal

total mesorectal excision in rectal cancer: a comparison of 115 cases. European Journal of Surgical Oncology. DOI: 10.1016/j.ejso.2017.11.011.

25. Sung S-Y, Kim SH, Lee JH, Nam TK, Jeong S, Jang HS, Song JH, Lee JW, Bae JM, Lee JH. Continuous effect of radial resection margin on recurrence and survival in rectal cancer patients who receive preoperative chemoradiation and curative surgery: a multicenter retrospective analysis. Int J Radiat Oncol Biol Phys 2017; 98(3): 647-653.
26. Crippa J, Grass F, Dozois EJ, Mathis KL, Merchea A, Colibaseanu DT, Kelley SR, Larson DW. Robotic Surgery for Rectal Cancer Provides Advantageous Outcomes Over Laparoscopic Approach: Results From a Large Retrospective Cohort. Ann Surg. 2020 Feb 14. doi: 10.1097/SLA.0000000000003805. Epub ahead of print. PMID: 32068552.
27. Prete FP, Pezzolla A, Prete F, Testini M, Marzaioli R, Patriti A, Jimenez-Rodriguez RM, Gurrado A, Strippoli GFM. Robotic Versus Laparoscopic Minimally Invasive Surgery for Rectal Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Ann Surg. 2018 Jun;267(6):1034-1046. doi: 10.1097/SLA.0000000000002523. PMID: 28984644.
28. Gavriilidis P, Wheeler J, Spinelli A, de'Angelis N, Simopoulos C, Di Saverio S. Robotic vs laparoscopic total mesorectal excision for rectal cancers: has a paradigm change occurred? A systematic review by updated meta-analysis. Colorectal Dis. 2020 Apr 25. doi: 10.1111/codi.15084. Epub ahead of print. PMID: 32333491.
29. Jayne D, Pigazzi A, Marshall H, Croft J, Corrigan N, Copeland J, Quirke P, West N, Edlin R, Hulme C, Brown J. Robotic-assisted surgery compared

with laparoscopic resection surgery for rectal cancer: the ROLARR RCT. Southampton (UK): NIHR Journals Library; 2019 Sep. PMID: 31556981.

30. Sun Y, Xu H, Li Z, Han J, Song W, Wang J, Xu Z. Robotic versus laparoscopic low anterior resection for rectal cancer: a meta-analysis. World J Surg Oncol. 2016 Mar 1;14:61. doi: 10.1186/s12957-016-0816-6. PMID: 26928124; PMCID: PMC4772524.
31. Kim YW, L H, Kim NK, Min BS, Lee KY. The learning curve for robot-assisted total mesorectal excision for rectal cancer. Surg Laparosc Endosc Percutan Tech 2012; 22(5): 400-405
32. Bokhari MB, P C, Ramos-Valadez DI, Ragupathi M, Haas EM. Learning curve for robotic assisted laparoscopic colorectal surgery. Surg Endosc 2011;25(3): 855-860.
33. Jimenez-Rodriguez RM, D-PJ, de la Portilla de Juan F, Prendes-Sillero E, Dussort HC, Padillo J. Learning curve for robotic-assisted laparoscopic rectal cancer surgery. Int J Colorectla Dis 2013; 28(6): 815-821.
34. Hirst A, Philippou Y, Blazeby J, Campbell B, Campbell M, Feinberg J, Rovers M, Blencowe N, Pennell C, Quinn T, Rogers W, Cook J, Kolias AG, Agha R, Dahm P, Sedrakyan A, McCulloch P. No Surgical Innovation Without Evaluation: Evolution and Further Development of the IDEAL Framework and Recommendations. Ann Surg. 2019 Feb;269(2):211-220. doi: 10.1097/SLA.0000000000002794. PMID: 29697448.
35. Hellan M, Ouellette J, Lagares-Garcia JA, Rauh SM, Kennedy HL, Nicholson JD, Nesbitt D, Johnson CS, Pigazzi A. Robotic Rectal Cancer Resection: A Retrospective Multicenter Analysis. Ann Surg Oncol. 2015 Jul;22(7):2151-8. doi: 10.1245/s10434-014-4278-1. Epub 2014 Dec 9. PMID: 25487966.

36. Baek SJ, Kim CH, Cho MS, Bae SU, Hur H, Min BS, Baik SH, Lee KY, Kim NK. Robotic surgery for rectal cancer can overcome difficulties associated with pelvic anatomy. Surg Endosc. 2015 Jun;29(6):1419-24. doi: 10.1007/s00464-014-3818-x. Epub 2014 Aug 27. PMID: 25159651.
37. Park JS, Kim NK, Kim SH, Lee KY, Lee KY, Shin JY, Kim CN, Choi GS; Korean Laparoscopic Colorectal Surgery Study Group. Multicentre study of robotic intersphincteric resection for low rectal cancer. Br J Surg. 2015 Nov;102(12):1567-73. doi: 10.1002/bjs.9914. Epub 2015 Aug 27. PMID: 26312601.
38. Valverde A, Goasguen N, Oberlin O, Svrcek M, Fléjou JF, Sezeur A, Mosnier H, Houdart R, Lupinacci RM. Robotic versus laparoscopic rectal resection for sphincter-saving surgery: pathological and short-term outcomes in a single-center analysis of 130 consecutive patients. Surg Endosc. 2017 Oct;31(10):4085-4091. doi: 10.1007/s00464-017-5455-7. Epub 2017 Mar 7. Erratum in: Surg Endosc. 2017 Jun 23;: PMID: 28271268.

References part 2

1. Wang C, Zhai H, Liu W, Li J, Yang J, Hu Y, Huang J, Yang W, Pan Y, Ding H (2014) Thyroidectomy: a novel endoscopic oral vestibular approach. Surgery 155(1): 33-38.
2. Anuwong A (2016). Transoral endoscopic thyroidectomy vestibular approach: a series of the first 60 human cases. World J Surg 40(3): 491-497

3. Inabnet WB 3rd, Fernandez-Ranvier G, Suh H (2018) Transoral endoscopic thyroidectomy-an emerging remote access technique for thyroid excision. Jama Surg 153(4): 376-377.
4. Ma X, Xia Q, Li G, Wang T, Li Q (2017) Aesthetic principles access thyroidectomy produces the best cosmetic outcomes as assessed using the patient and observer scar assessment scale. BMC Cancer 17: 654-661.
5. Zhang D, Park D, Sun H, Anuwong A, Tufano R, Kim HY, Dionigi G (2019) Indications, benefits and risks of transoral thyroidectomy. Best Pract Res Clin Endocrinol Metab, doi.org/10.1016/j.beem.2019.05.004
6. Perigli G, Cortesini C, Qirici E, Boni D, Cianchi F (2008) Clinical benefits of minimally invasive techniques in thyroid surgery. World J Surg 32(1): 45-50.
7. Perigli G, Qirici E, Badii B, Kokomani A, Staderini F, Luconi M, Crescioli C, Mannelli M, Maggi M, Cianchi F (2013) Feasibility and safety of minimal-incision thyroidectomy for Grave's disease: a prospective, single-center study. Head Neck 35(9): 1345-1348.
8. Feldman JJ (2014) Neck lift my way: an update. Plast Reconstr Surg 134: 1173-1183
9. Razavi CR, Tufano RP, Russell JO (2019) Starting a Transoral Thyroid and Parathyroid Surgery Program. Curr Otorhinolaryngol Rep. DOI: 10.1007/s40136-019-00246-w
10. Razavi CR, Vasiliou E, Tufano RP, Russell JO (2018) Learning Curve for Transoral Endoscopic Thyroid Lobectomy. Otolaryngol Head Neck Surg. 159(4):625-629.

11. Anuwong A, Ketwong K, Jitpratoon P, Sasanakietkul T, Duh QY (2018) Safety and outcomes of the transoral endoscopic thyroidectomy vestibular approach. JAMA 153(1): 21-27
12. Celik S, Makay O, Yoruk MD, Bayzit Kocer I, Ozdemir M, Kilic KD, Tomruk C, Bilge O, Uyanikgil Y, Dionigi G (2019) A surgical and anatomo-histological study on Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA). Surg Endosc. doi: 10.1007/s00464-019-06856-1