ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ:
“ΕΛΑΧΙΣΤΑ ΕΠΕΜΒΑΤΙΚΗ ΧΕΙΡΟΥΡΓΙΚΗ,
ΡΟΜΠΟΤΙΚΗ ΧΕΙΡΟΥΡΓΙΚΗ ΚΑΙ ΤΗΛΕΧΕΙΡΟΥΡΓΙΚΗ”

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ: MINIMALLY INVASIVE LYMPHADENECTOMY IN CERVICAL CANCER

ΜΕΤΑΠΤΥΧΙΑΚΗ ΦΟΙΤΗΤΡΙΑ:
ΡΙΖΟΥ ΑΝΑΣΤΑΣΙΑ
Α.Μ.: 20130762

ΑΘΗΝΑ, ΣΕΠΤΕΜΒΡΙΟΣ 2016

ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ
ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ
ΓΙΑ ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ
Της Μεταπτυχιακής Φοιτήτριας ΡΙΖΟΥ ΑΝΑΣΤΑΣΙΑΣ

Εξεταστική Επιτροπή

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- Χρήστος Π. Τσιγκρής, Ομότιμος Καθηγητής Χειρουργικής & Επιστημονικός Υπεύθυνος του Π.Μ.Σ.
- Θεόδωρος Διαμαντής, Καθηγητής Χειρουργικής

Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε από την ΓΣΕΣ της Ιατρικής Σχολής του Παν. Αθηνών Συνεδρίαση της.....ης ..... 20.... για την αξιολόγηση και εξέταση της υποψηφίου κας Ρίζου Αναστασίας, συνεδρίασε σήμερα .../.../....

Η Επιτροπή διαπίστωσε ότι η Διπλωματική Εργασία της Κας Ρίζου Αναστασίας με τίτλο: ΄΄Minimally Invasive Lymphadenectomy in Cervical Cancer΄΄, είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη.

Η εξεταστική επιτροπή αφού έλαβε υπ' όψιν το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους ..... προτείνει την απονομή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's Degree), στον παραπάνω Μεταπτυχιακό Φοιτητή.

Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους ....., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ....., και για τον βαθμό «ΚΑΛΩΣ» ψήφους ..... Κατά συνέπεια, απονέμεται ο βαθμός «.....».

Τα Μέλη της Εξεταστικής Επιτροπής

- Αλέξανδρος Παπαλάμπρος **(Επιβλέπων)** (Υπογραφή) _____
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- Θεόδωρος Διαμαντής (Υπογραφή) _____

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INTRODUCTION

Despite the great improvements in the diagnosis and treatment of cervical cancer, it is both the fourth-most common cause of cancer and the fourth-most common cause of death from cancer in women[1]. In 2012, an estimated 528,000 cases of cervical cancer occurred, with 266,000 deaths[1]. This is about 8% of the total cases and total deaths from cancer with most cases occurring in developing countries[2]. Cervical cancer diagnosis is made by cervical biopsy or conization. It is important to estimate the extent of the disease not only for prognostic purposes, but also for treatment planning. Cervical cancer is staged by the International Federation of Gynecology and Obstetrics (FIGO) staging system (Table 1) , which is based on clinical examination, rather than surgical findings. The FIGO stage of disease is not changed by surgicopathologic findings of metastatic disease at the time of radical hysterectomy or lymphadenectomy, although lymph node metastasis is an important prognostic factor and may alter therapy.[3],[4],[5]

FIGO Stage	**Definition**
Stage 0	Carcinoma in situ
Stage I	Cervical carcinoma confined to the cervix (extension to the corpus should be disregarded)
Stage IA	Invasive cevical cancer diagnosed by microscopy only
Stage IA1	Stromal invasion no deeper than 3 mm, no wider than 7 mm in horizontal spread
Stage IA2	Stromal invasion >3 but no more than 5 mm and no wider than 7 mm in horizontal spread
Stage IB	Clinically visible lesion confined to the cervix or microscopic disease greater than stage IA
Stage IB1	Clinically visible lesion <4 cm
Stage IB2	Clinically visible lesion >4 cm
Stage II	Tumor extends beyond uterus but not to pelvic sidewall or lower third of vagina
Stage IIA	Vaginal involvement without parametrial involvement
Stage IIA1	Clinically visible lesion <4 cm
Stage IIA2	Clinically visible lesion >4 cm
Stage IIB	Parametrial involvement
Stage III	Tumor extends to pelvic sidewall and/or causes hydronephrosis and/or extends to lower third of vagina
Stage IIIA	Involvement of lower third of vagina with no extension to sidewall
Stage IIIB	Extension to pelvic sidewall and/or hydronephrosis
Stage IV	Extension beyond the true pelvis or into mucosa of rectum or bladder
Stage IVA	Extension into adjacent organs
Stage IVB	Distant metastases

Table 1: 2009 International Federation of Gynecology and Obstetrics (FIGO) staging of cervical cancer

Abdominal radical hysterectomy (ARH) has been the primary treatment for early stage invasive cervical cancer, with some modifications of the method along the years. It was first described by Wertheim[6] of Vienna in 1898 and since Meigs[7] began to perform radical hysterectomy with pelvic lymphadenectomy in 1951 there were no major changes in surgical technique.

Minimal invasive surgery has been regularly used by gynecologists for several decades. The objective of using a minimally invasive approach for the treatment of cervical cancer has been to decrease perioperative morbidity and to improve surgical and oncological outcomes. Since Nezhal et al.[8] and Canis et al.[9] suggested total laparoscopic radical hysterectomy with pelvic lymphadenectomy (TLRH) for the treatment of cervical cancer, several reports has shown its safety and feasibility [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21]. Reported advantages include less blood loss, shorter length of hospital stay, less postoperative pain and postoperative complications [8], [9], [10], [13], [14]. Nevertheless, the TLRH has not been widely adopted in surgical practice, because of technical limitations such as a long learning curve, 2-dimensional visualization with reduced depth perception, rigid instruments, ergonomic difficulty and tremor amplification [17], [18], [22].

More recently, the development of the Da Vinci system (da Vinci Surgical System, Intuitive Surgical Inc., CA, USA) in the mid 2000s provided a high-definition-3-D vision system, tremor filtration, seven degrees of motion ("wristed movement""), improved ergonomics and faster suturing. Furthermore, robotic-assisted surgical technique has shown to require a shorter learning curve compared to conventional laparoscopy [23], [24], [25], [26]. However, robot-assisted surgery also has its limitations, such as the absence of touch sensation and increased costs.

In 2005, the da Vinci system was Food and Drug Administration cleared for hysterectomy procedures [27] and in 2006, the first robot-assisted laparoscopic radical hysterectomy (RRH) for cervical cancer was reported by Bilal M. Sert[28]. Several larger case series followed, demonstrating feasibility and potential benefits of RRH [29], [30], [31], [32], [33]. As a result, the integration of robotic technology into laparoscopic surgery is used with increasing frequency. The aim of this study is to review the current literature on both laparoscopic and robot-assisted lymphadenectomy in the treatment of cervical cancer.

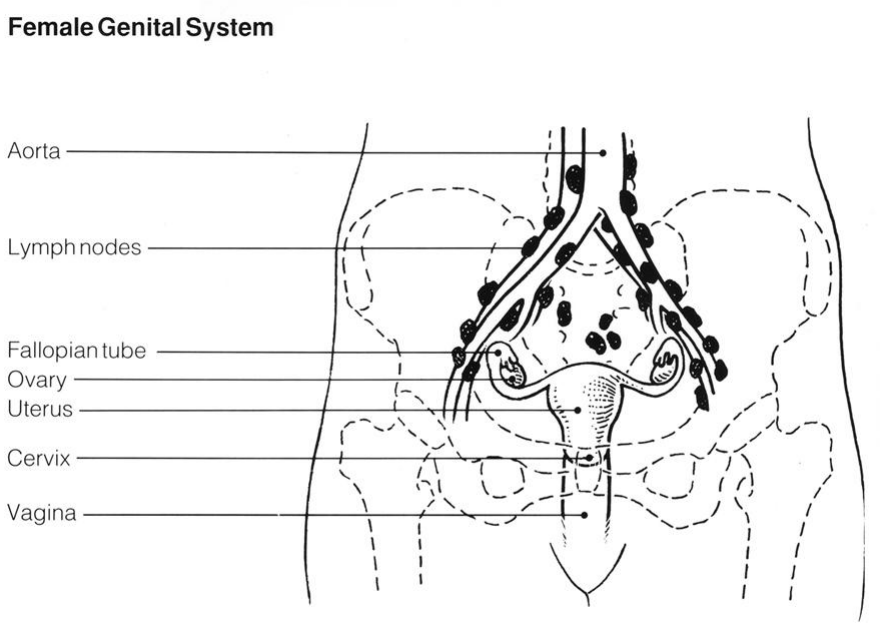

Figure 1: Female Genital System

Pelvic Lymph Node Dissection. Frank Papanikolaou et al. Medscape: Dec 27, 2015

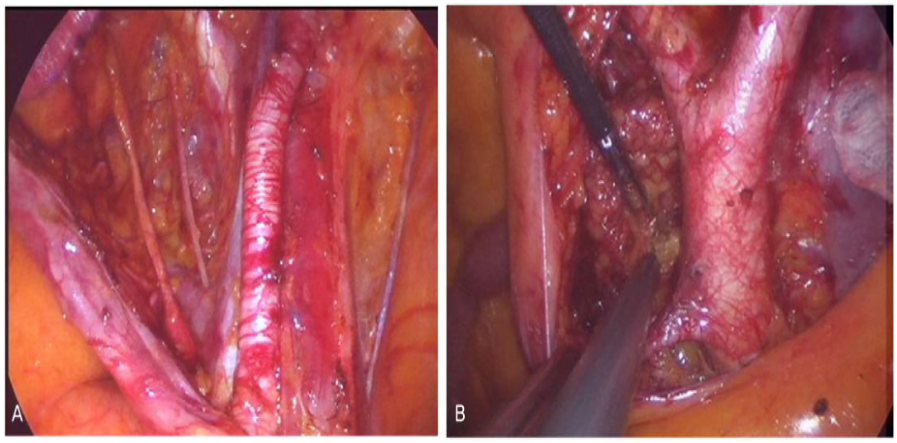

Figure 2: Intraoperative view (A)laparoscopic pelvic lymph node dissection, (B)laparoscopic paraaortic lymph node dissection. Young Eun Jeon et al. Two-port access laparoscopic radical hysterectomy: First clinical report.*J Womens Med. 2010 Mar;3(1):18-22.*

Figure 3: Intraoperative view after completing left side para-aortic node dissection to left renal vein level. Left renal vein is seen at left side to the suction.. Robotic high para-aortic lymph node dissection with high port placement using same port for pelvic surgery in gynecologic cancer patients. Tae-Joong Kim et al. J Gynecol Oncol. 2015 Jul;26(3):222-226.

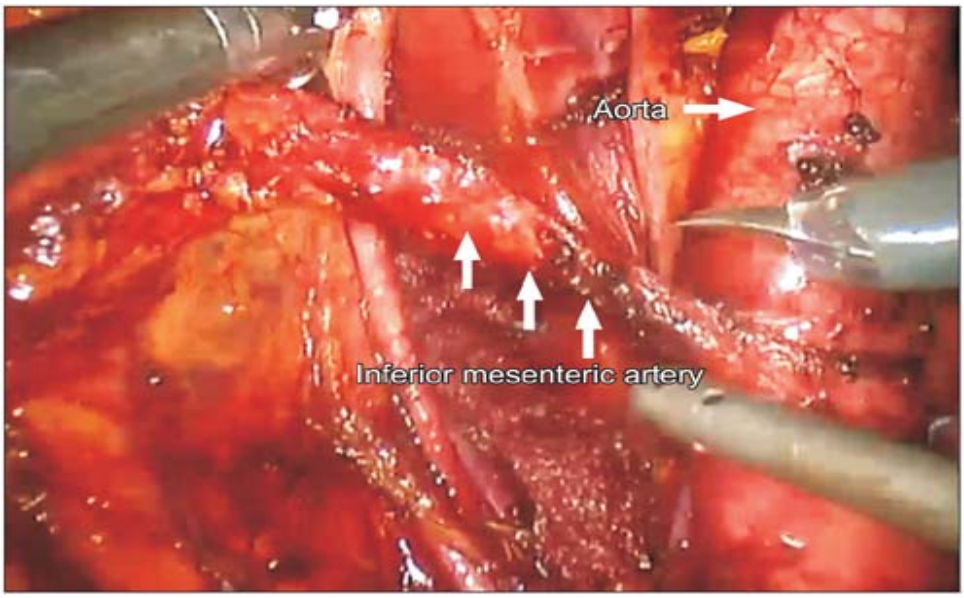

Figure 4: Intraoperative view after completing left side robotic para-aortic lymph node dissection to inferior mesenteric artery level. Robotic high para-aortic lymph node dissection with high port placement using same port for pelvic surgery in gynecologic cancer patients. *Tae-Joong Kim et al. J Gynecol Oncol. 2015 Jul;26(3):222-226.*

Materials and Methods

Literature search

A PubMed, Embase and Cochrane Library database search was performed on literature published from 2007 to 2016. Only articles published in English and procedures performed by laparoscopic or robot approach were included in this study. The following terms were used to perform the research: "cervical cancer", "laparoscopy" or laparoscopic", "robot" or "robotic" or "da Vinci", "minimally invasive", "radical hysterectomy", "pelvic lymphadenectomy" and "para-aortic lymphadenectomy".

Method of review

A total of 43 trials was identified. 11 had overlapping data: in that case only the study with the most recent information was included in the analysis. A total of 17 studies were included for analysis.

The following parameters were extracted from each study to analyze: study features (first author, year of publication, study design), surgical and pathological parameters (age, body mass index, conversion rate). Data on operative time, estimated blood loss, number of retrieved lymph nodes, length of hospital stay, complications, positive lymph nodes, conversion to laparotomy, recurrence and morbidity were also extracted.

Inclusion criteria

For inclusion in the meta-analysis, a study had to fulfil the following criteria: (a) analyze the outcomes of robotic or laparoscopic lymphadenectomy for cervical cancer, (b) report on at least one of the outcome measures mentioned below, (c) if multiple studies were reported by the same institution, the most recent publication was included in the analyses.

Exclusion criteria

(a) Abstracts, letters and expert opinions were excluded, (b) studies that reported on minimally invasive lymphadenectomy for benign lesions or for other types of gynecological cancer, (c) overlap between authors or centers in the published literature.

Results

Study Characteristics

In this study 17 trials from the initial literature were included published between 2007 and 2016 with a total of 1676 participants. 837 patients underwent total robotic or robot-assisted surgery, 406 underwent total laparoscopy and 433 laparotomy. 6 of the studies were conducted in USA, 1 both in USA and Norway, 2 in Netherlands, 2 in Italy, 2 in Belgium, 1 in Korea, 1 in Spain and 2 in France. When pelvic or para-aortic lymphadenectomy was performed as the only surgical procedure, it is referred to as “isolated,” and when it was associated with hysterectomy, it is described to as “combined.” Usually, pelvic and/or para-aortic lymphadenectomy follows a radical hysterectomy. Thus, most studies present both precedures’ results.

Publication	Study design	Country	Journal Year	Stydy Period
Sert[34]	Retrospective multi-center study	Oslo, Norway/Chapper Hill, NC and Orlando, FL, USA	2016	2005-2011
Hoogendam[35]	Observational cohort study	Utrecht, Netherlands	2014	2008-2013
Maggioni[36]	A case control study	Milan, Italy	2009	2006-2009
Fastrez[37]	Retrospective multi-center study	Brussels/ Liege/ Leuven, Belgium	2013	2007-2011
Lambaudie[38]	Retrospective case series	Marseille/Lille, France	2010	2007-2010
Tinelli[39]	Retrospective study	Avelinno, Italy	2011	2003-2010
Nezhat[40]	Prospective nonrandomized analysis	New York, USA	2008	2000-2008
Lowe[33]	Retrospective study	Chicago.USA	2009	2003-2008
Cantrell[41]	Retrospective analysis	North Carolina, USA	2010	2005-2008
Segaert[42]	Retrospective multi-center study	Belgium	2015	2007-2014
Schreuder[43]	Retrospective review	Netherlands	2010	2004-2008
Ramirez[44]	Retrospective review	Texas, USA	2008	2006-2008

Boggess[24]	Case-control study	North Carolina, USA	2008	2005-2007
Kim[30]	Retrospective clinical review	Seoul, Korea	2008	2006-2007
Estape[45]	Case matched analysis	USA	2009	2002-2008
LeBlanc[46]	Retrospective study	Lille, France	2007	1997-2004
Diaz-Feijoo[47]	Retrospective review	Barcelona, Spain	2014	2009-2013

Table 2: Study characteristics

Publication	**Number of patients**	**Approach**	**Type of surgery**
Sert[34]	491	Total robotic (259)/ Laparotomy (232)	Radical hysterectomy with pelvic lymphadenectomy
Hoogendam[35]	100	Robot assisted laparoscopic	Pelvic lymphadenectomy ± radical hysterectomy or radical trachelectomy
Maggioni[36]	80	Total robotic (40)/ Laparotomy (40)	Radical hysterectomy with pelvic lymphadenectomy
Fastrez[37]	37	Robot-assisted laparoscopic	Transperitoneal or retroperitoneal para-aortic lymphadenectomy
Lambaudie[38]	58	Robot assisted laparoscopy (22)/ Total laparoscipic (16)/ Laparotomy (20)	Pelvic+para-aortic lymphadenectomy ± simple colpohysterectomy or radical hysterectomy with
Tinelli[39]	99	Total laparoscopic (76)/ Total robotic (23)	Radical hysterectomy with pelvic lymphadenectomy ± para-aortic lymphadenectomy
Nezhat[40]	43	Total laparoscopic (30)/ Total robotic (13)	Radical hysterectomy with pelvic lymphadenectomy
Lowe[33]	42	Robotic assisted laparoscopy	Radical hysterectomy with pelvic lymphadenectomy
Cantrell[41]	127	Total robotic (63)/ Laparotomy (64)	Radical hysterectomy with pelvic lymphadenectomy
Segaert[42]	109	Robot-assisted laparoscopic	Radical hysterectomy with pelvic lymphadenectomy
Schreuder[43]	28	Total robotic (14)/ Open (14)	Radical hysterectomy with pelvic lymphadenectomy
Ramirez[44]	5	Total robotic	Radical parametrectomy & bilateral pelvic lymphadenectomy
Boggess[24]	100	Robotic-assisted (51)/ Open (49)	Radical hysterectomy with pelvic lymphadenectomy

Kim[30]	10	Total robotic	Radical hysterectomy with pelvic lymphadenectomy
Estape[45]	63	Open (14)/ Total laparoscopic (17)/ Robotic assisted (32)	Radical hysterectomy with pelvic lymphadenectomy± para-aortic lymphadenectomy
LeBlanc[46]	184	Total laparoscopic	Extraperitoneal bilateral infrarenal paraortic lymph node dissection
Diaz-Feijoo[47]	100	Robotic-assisted laparoscopy(17)/Total laparoscopic (83)	Extraperitoneal paraaortic lymphadenectomy

Table 3: Study characterisrics

Clinicopathological characteristics

The general characteristics of the surgical groups are shown in Table 4. The mean age of patients at surgery was 41.5 for robotic approach group, 46.2 for laparoscopic group and 50.1 for laparotomic group . The BMI status was reported in all studies and did not differ significantly between the surgical groups.

Publication	**Age (range)**	**BMI[kg/m^2] (range)**	**FIGO stage ≤IB1: ≥IB2**	**Follow up [months] (range)**
Sert[34]	44.5 ± 11.7/ --------/ 46.7 ± 12.2 {p 0.04}	27.6 ± 6.5/ ----------/ 27.4 ± 6.6 {p 0.89}	242:17/ ------/ 205:24	34.6 ± 21.7/ ----------/ 45.2 ± 28.5 {p<0.001}
Hoogendam[35]	41 (23-81)/ --------/ ---------	23.2 (18.3-35.1)/ ----------/ ----------	90:10/ -----/ -----	29.5(2.5±67.1)/ ----------/ ----------
Maggioni[36]	44.1 ± 9.1/ ----------/ 49.8 ± 14.1 {p 0.035}	24.1 ± 5.5/ ----------/ 23.6 ± 5 {p 0.669}	30:10/ ------/ 26:14	NR
Fastrez[37]	58 (38-78)/ ---------/ ---------	24.3 (17.3-31.3)/ ----------/ ----------	0:8/ ----/ -----	NR
Lambaudie[38]	50.5 (36-64)/ 45 (32-57)/ 53 (31-72) {p 0.05}	22 (17.8-38.6)/ 21.9 (14.3-39.4)/ 21.9 (17.2-34) {p NS}	2:20/ 1:15/ 0:20	11.55(3.5-22.5)/ 19.45 (2.4-50)/ 34.6(15.8-84.4) {p<0.001}
Tinelli[39]	43.1 ± 8.9/ 41.9 ± 7.1/	28 ± 4/ 29 ± 3/	21:2/ 69:7/	24.5 (2-48)/ 46.5 (3-90)/

	---------- {p NS}	------ {p NS}	----- {p NS}	----------
Nezhat[40]	54.8 (39-78)/ 46.8 (29-63)/ ---------- {p NR}	NR	11:2/ 26:4/ ----- {p NR}	12/ 29/ ---- {p NR}
Lowe[33]	41/ ---/ ---	25.1/ ----/ ----	36:6/ -----/ -----	NR
Cantrell[41]	43 (17-75)/ ---------/ 41.5 (20-72) {p 0.39}	28 (18-49)/ ----------/ 25 (19-37) {p 0.33}	58:5/ ----/ 56:8 {p 0.25}	12.2 (0.2-36.3)/ ---------------/ 28 {p NR}
Segaert[42]	---------/ 40.8(28.4-63.4)/ 42.5 (27.3-68.3) {p 0.44}	----------/ 28.1 (18.4-40.8)/ 28.2 (17.4-46.4) {p 0.95}	--------/ 35:0/ 53:1 {p 0.88}	----/ 7.2/ 15.2 {p NR}
Schreuder[43]	43 (31-78)/ ---------/ 46 (32-68) {p NR}	NR	11:1/ -----/ 13:1 {p NR}	26 (17-32)/ ----------/ 42 (31-54) {p NR}
Ramirez[44]	42 (38-52)/ ----------/ ----------	23.8 (17.7-26.5)/ ---------------/ ---------------	5:0/ ---/ ---	7.5 (1.3-13.8)/ --------------/ --------------
Boggess[24]	47.4 ± 12.9/ ----------/ 41.9 ± 11.2 {p 0.029}	28.6 ± 7.2/ ----------/ 26.1 ± 5.1 {p 0.08}	43:8/ ----/ 44:5 {p 0.32}	NR
Kim[30]	49.9 (34-75)/ ----------/ ----------	26.34 (20.3-31.6)/ ----------/ ----------	10:0/ ----/ ----	9/ ----/ ----
Estape[45]	55 (33-83)/ 52.8 (37-83)/ 42 (27-71) {p NS}	29.7 (24.8-36.3)/ 28.1 (20.8-36.8)/ 29.5 (20.1-44.3) {p NS}	29:3/ 16:1/ 13:1 {p NS}	284.2±152.1(days)/ 941.6 ± 273.9/ 1382.4 ± 592.7 {p<0.0001}
LeBlanc[46]	---/ 45 (25-75)/ ---	---/ 27.1 (16.8-41)/ ---	---/ 0:179(5 recurrent)/ --	---/ 32.9 (3-89)/ ---
Diaz-Feijoo[47]	49 (29-66)/ 51 (24-74)/ --- {p 0.38}	23 (16-32)/ 26.5 (18-44)/ --- {p 0.04}	0:17/ 0:83/ --- {p NR}	13.4 (1-40.5)/ NR/ --- {p NR}

Table 4: Clinicopathological characteristics (Robotic / Laparocopic / Laparotomy approach)

Lymphadenectomy outcomes

All studies report the number of ressected lymph nodes. One study (Maggioni) revealed significant larger number of removed lymph nodes in the laparotomy group and four in the robotic group (Estape, Cantrell, Boggess, Diaz-Feijoo). Lymph node metastasis was documented in 12 trials and lymphatic complications in 13, but none of them proved significant difference between the 3 groups.

Publication	Positive Lymphovascular Space Invasion (LVSI)	No of lymph nodes removed	No of positive nodes	Lymphatic complications
Sert[34]	88/ ---/ 92 {p 0.35}	<20:96->20:163/ -----/ <20:94->20:134 {p 0.35}	25 (12%)/ ----/ 29 (10%) {p 0.49}	9/ ---/ 12
Hoogendam[35]	46/----/----	24 (10-56)/----/-----	10/---/---	9/---/----
Maggioni[36]	NR	20.4 ± 6.9/ ----------/ 26.2± 11.7 {p 0.05}	NR	1/ ---/ 6 {p 0.113}
Fastrez[37]	NR	27.5 (1-54)/ ----/ ----	5patients(13.5%)/ ---/ ----	NR
Lambaudie[38]	NR	9/7.5/12 {p NS}	2/2/2 {p NS}	4/1/0 {p NS}
Tinelli[39]	NR	Pelvic: 24.7±5.2/ 27.1±4.7/ ------ {p 0.49} Aortic:10.2±2.8/ 11.5±1.8/	2 patients / 9 patients/ ----------	2 (8.6%)/ 9 (11.8%)/ -------

		------ {p 0.38}		
Nezhat[40]	9/16/-----	24.7(11-51)/31(10-61)/-- {p NS}	1/3/------	1/0/----
Lowe[33]	NR	25 (12-60)/ ------/ ------	12%of all patients/ ----/ ------	0/ ----/ -----
Cantrell[41]	NR	29 (13-99)/ ----------/ 24 (4-72) {p 0.04}	5 (8%)/ --------/ 9 (14%)	NR
Segaert[42]	30/---/----	23 (6-70)/------/-------	NR	0/---/----
Schreuder[43]	NR	29 (19-76)/ ----------/ 26 (10-41) {p 0.064}	NR	NR
Ramirez[44]	4(80%)/---/--	14 (6-16)/-------/-------	0/-----/------	1/----/-----
Boggess[24]	NR	33.8±14.2/----/23.3±12.7 {p 0.0003}	NR	1/----/1
Kim[30]	NR	27.6(12-52)/----/-----	0/----/----	0/-----/------
Estape[45]	NR	32.4±10/ 18.6±5.3/ 25.7±11.5	NR	NR
LeBlanc[46]	NR	–/ 20.8 (1-52)/ --	–/ 44patients (24.3%)/ --	---/ 20patients (10/9%)/ ---
Diaz-Feijoo[47]	NR	17 (10-31)/ 14 (4-62)/	1 patient (5.9%)/ NR/	3 (17.6%)/ NR/

		--- {p< 0.05}	--- {p NR}	--- {p NR}

Table 5: Lymphadenectomy outcomes (Robotic / Laparocopic / Laparotomy approach)

Operative outcomes

The mean operation time has been provided by all of the studies. It varies between 144 and 434 min for robotic approach group, between 132 and 318 min for laparoscopic group and between 114 and 247.8 min for laparotomic group. Two of them (Cantrell, Boggess) showed significant longer operative time in the laparotomy group, one (Lambaudie) in the laparoscopic group and four (Schreuder, Sert, Maggioni, Tinelli) in the robotic group.

The estimated blood loss (EBL) was found in 16 studies, seven of which have shown significant lower blood loss in the robotic group. Mean EBL ranged from 20 to 355 ml in the robotic group, from 90 to 209.4 ml in the laparoscopic group and from 221.8 to 2000 ml in the laparotomy group.

Transfusion rate was recorded in 15 studies and was proved significantly lower in robotic group in two studies (Sert, Estape).

Conversion rate was documented in 15 studies and ranged from 0% to 5.3%.

Publication	**Mean operation time (minutes)**	**Estimated blood loss (ml)**	**Transfusion rate**	**Conversion rate**
Sert[34]	220±53/-----/156±57 {p <0.001}	<150ml: 206±80/----/10±4 ≥150ml: 53±20/---/222±96 {p<0.001}	Significantly lower in the RRH group	NR
Hoogendam[35]	319(175-472)/ ---/ ---	185/ ----/ -----	0/ ----/ ----	1(laparoscopy)/ ----/ -----

Maggioni[36]	272.27±42.3/ ----------/ 199.6±65.6 {p<0.001}	78±94.8/ ----------/ 221.8±132.4 {p<0.001}	3/ -----/ 9 {p 0.117}	0/ ---/ ---
Fastrez[37]	200 (60-340))/---/---	Median haemoglobin fall 1.36g/dl (0-2.7)	1/---/----	1/---/----
Lambaudie[38]	210 (120-330)/ 267.5 (165-420)/ 210 (135-330) {p 0.01}	NR	1/ 0/ 1 {p NS}	0/ 0/ -
Tinelli[39]	323±30/255±25/----- {p 0.05}	157±7/95±5/------ {p NS}	0/0/-----	0/0/----
Nezhat[40]	323 (232-453)/ 318 (200-464)/ ---------- {p NS}	157 (50-400)/ 200 (100-500)/ ---------- {p NS}	0/ 0/ ----	0/ 0/ -----
Lowe[33]	215(120606)/----/---	50 (25-150)/---/---	0/---/----	1/---/----
Cantrell[41]	213 (75-290)/ ----------/ 240 (181-420) {p 0.0015}	50 (20-400)/ ----------/ 400 (100-1200) {p<0.0001}	NR	NR
Segaert[42]	281 (160-550)/ ----------/ ----------	150 (15-1500)/ ----------/ ----------	11/ ---/ ---	0/ ---/ ---

Schreuder[43]	434 (264-610)/ ----------/ 225 (170-330) {p<0.001}	300 (50-1000)/ ----------/ 2000 (1000-4.600) {p<0.001}	NR	0/ --/ --
Ramirez[44]	365(331-430)/---/---	100(50-175)/---/---	0/--/--	0/--/--
Boggess[24]	210.9±45.5/ ----------/ 247.8±48.8 {p 0.0002}	96.5±85.8/ ----------/ 416.8±188.1 {p 0.0001}	0/ -----/ 4 {p 0.15}	0/ ----/ -
Kim[30]	207(120-240)/---/---	355/---/---	0/---/---	0/---/---
Estape[45]	2.4h±0.8h/ 2.2h±0.7h/ 1.9h±0.6h {p NS}	130±119.4/ 209.4±169.9/ 621.4±294.0	1/ 0/ 5	0/ 0/ --
LeBlanc[46]	–/155(90-280)/--	---/100(25-500)/---	–/0/---	–/0/--
Diaz-Feijoo[47]	150 (85-270)/ 150 (80-255)/ ---- {p 0.59}	20 (5-350)/ 90 (10-260)/ --- {p< 0.05}	0/ NR/ ---	0/ NR/ ---

Table 6: Operative outcomes (Robotic / Laparocopic / Laparotomy approach)

Post-operative outcomes

The postoperative morbidity rates were reported in 15 trials. None of them showed significant difference in favor of robotic group.

The overall mortality rates were reported in 12 studies. It ranged from 0% to 40% in the robotic group, from 0% to 11.8% in the laparoscopic group and from 0% to 20% in the open group but none of the comparative studies proved significant difference between them.

The mean length of postoperative hospital stay (LOS) was 2.78 days in the robotic group, 3 days in the laparoscopic group and 5 days in the open group. Six studies (Sert, Maggioni, Lambaudie, Cantrell, Schreuder, Boggess) reported significant shorter LOS for the robotic group.

The recurrence rate was found in 15 studies but none of them reported significant difference between groups.

Publication	Overall morbidity	Mortality	Length of hospital stay (days)	Recurrence rate
Sert[34]	75(3%)/ --/ 61(4%)	7/ --/ 9 {p 0.48}	≤3: 156/--/35 >3: 103/--/197 {p<0.001}	23(9%)/ --/ 21(9%) {p 1.00}
Hoogendam[35]	NR	7/--/--	4(2-8)/--/--	13(13%)/--/--
Maggioni[36]	45/ --/ 24	1/ --/ 0	3.7±1.2/ -------/ 5±2.4 {p<0.01}	5/ ---/ 5
Fastrez[37]	5 (13.5%)/---/---	15 (40%)/---/---	6(2-10)/--/--	17 (46%)/--/--
Lambaudie[38]	5(22.7%)/ 2(12.5%)/ 4(20%) {p NS}	2(9.1%)/ 2(11.8%)/ 4(20%) {p NS}	3(3-10)/ 4.5(3-8)/ 7(3-17) {p<0.01}	6(27.3%)/ 4(25%)/ 6(30%) {p NS}
Tinelli[39]	NR	NR	3±(1.2-7)/ 4±(2.3-7)/ ---------- {p NS}	1(4.4%)/ 4(5.4%)/ --- {p NS}
Nezhat[40]	4/ 6/ --- {p NS}	NR	2.7(1-6)/ 3.8(2-11)/ ---------- {p NS}	0/ 0/ --- {p NS}
Lowe[33]	5(12%)/--/--	NR	1/--/--	NR

Cantrell[41]	2/--/3	1/--/2 {p 0.47}	1(1-3)/---/4(3-8) {p<0.0001}	1/--/7 {p 0.27}
Segaert[42]	24 (22%)/--/--	6 (5.5%)/---/--	4.5 (3-19)/--/--	18 (16.5%)/--/--
Schreuder[43]	1/ –/ 3	NR	4(2-14)/ ----------/ 9(7-16) {p<0.001}	2/ –/ 1
Ramirez[44]	2/--/--	0/--/--	1(1-2)/--/--	0/--/--
Boggess[24]	4(7.8%)/ ----/ 8(16.3%) {p 0.35}	NR	1/ ---/ 3.2 {p<0.0001}	NR
Kim[30]	1/---/---	0/---/---	7.9(5-17)/---/---	0/---/---
Estape[45]	6(18.8%)/ 4(23.5%)/ 4(28.6%) {p NS}	0/ 0/ 2(14.3%) {p NS}	2.6±2.1/ 2.3±1.4/ 4.0±1.7 {p NS}	1(3.2%)/ 0/ 2(14.3%) {p NS}
LeBlanc[46]	–/ 1 patient/ --	–/ 0/ --	–/ 1.4/ --	–/ 67patients (36.4%)/ --
Diaz-Feijoo[47]	3 (17.6%)/ 7 (8/4%)/ --- {p 0.23}	5 (29.4%)/ NR/ -- {p NR}	2/ 2/ -- {p 0.22}	1 (5.9%)/ NR/ --- {p NR}

Table 7: Postoperative outcomes (Robotic / Laparocopic / Laparotomy approach)

Discussion

Radical hysterectomy with pelvic lymphadenectomy has been the primary treatment for cervical cancer since the mid 20th century. Minimally invasive surgery via laparoscopy has been pursued by gynecologists since 1990s. A number of studies have demonstrated its advantages over laparotomy which include decreased blood loss, shorter recovery time, shorter hospitalization and improved quality of life [48], [49].Nevertheless, laparoscopic approach has not received widespread adoption due to its disadvantages such as 2-dimensional visualization, limited range of motion, reduced depth perception and a long learning curve [50].

More recently, robotic technology has facilitaded the application of minimally invasive surgery. Its use in oncologic procedures has been increased since the first robotic radical hysterectomy with lymphadenectomy in 2006 [51], owing to advances in laparoscopic instruments [8], [9], [19], [52]. The da Vinci Surgical System provides a stable 3-dimensional vision, tremor filtration, wider range of motion with wristed instruments and a more ergonomic surgeon position [23], [30], [53], [54], [55].

Several studies have shown the feasibility and the safety of minimally invasive surgery in the treatment of cervical cancer, concerning both laparascopic and robotic approach [18], [19], [56]. However, some results are conflicting [10], [19], [20], [21]. Therefore, we reviewed the current literature with the aim to summarize the role of minimally invasive radical hysterectomy and lymphadenectomy in cervical cancer.

Our study includes 17 non-RCT trials which describe the results of either robotic or laparoscopic surgery in cervical cancer. Significant difference of characteristics such as age and BMI was found neither between the two groups nor in comparison with the laparatomy group.

The results concerning the operating time are controversial. Some studies showed that it was significantly longer in RL (robotic lymphadenectomy)([34],[36], [39], [43]), others found it was longer in AL (abdominal lymphadenectomy) ([24],[41]) and one ([38]) in LL (laparoscopic lymphadenectomy).This was associated with the learning curves, the experience of the surgeons and the time for setup which is not defined in most studies if it is included or not in the documented OT. Bogess et al. [24] performed a subanalysis on the operating time of RRH with lymphadenectomy in cervical cancer patients which revealed a decrease of 50 min between the first (243 min) and the ultimate 12 patients (193 min).

Estimated blood loss was found to be lower in robotic group in all comperative studies. The reasons for the redused blood loss include stable traction of robotic arms, an excellent 3D view and precise dissection with the robotic instruments.

The number of retrieved lymph nodes is a prognostic factor of oncological adequacy and long-term outcome of the procedure. Four studies indicate significantly larger number of removed lymph nodes in robotic group comparing to laparotomy and one comparing to laparoscopic approach. Nevertheless, none of these studies revealed significant difference regarding the number of positive lymph nodes or the percentage of lymphatic complications between the three groups.

The length of hospital stay is an important outcome variable, affecting patient satisfaction and cost analysis. In this review it became clear that the duration of hospital stay was significantly shorter in

robotic and laparoscopic treatment compared to laparotomy.

Analyzing morbidity after radical hysterectomy with pelvic lymphadenectomy , no major difference was found in literature between open and minimally invasive approach. The postoperative morbidity rate is usually used to assess the safety of such procedures. It ranged between 3-22.7% in robotic group and suggests that robotic approach could be considered as safe as open.

The recurrence and mortality rate are used to assess the feasibility of the procedure. Both were found similar in the three groups which proves the efficacy of minimally invasive approach in treatment of cervical cancer in comparison with open approach.

The present study has several limitations. First, it is not a meta-analysis in order to reveal more accurate conclusions. Second, all the included trials were observational and its results cannot be generalized to the extent that a randomized controlled trial could. Third, there was heterogeneity between the three groups, because it was impossible to match patient characteristics in all studies. Finally, between individual studies studies, follow-up time varied significantly.

In conclusion, although robot-assisted lymphadenectomy in cervical cancer is a technically demanding and time-consuming procedure, the results of this study suggest it may be an acceptable alternative to total laparoscopic or open approach, regarding surgical and short term oncological outcomes. Randomized controlled trials, including surgeons' ergonomics and costs, may give more definite results on the comparability of these three surgical techniques.

Abstract

Background
The aim of this study was to review the current literature on the role of minimally invasive lymphadenectomy in the treatment of cervical cancer.

Methods
Non Randomized Control Trials (NRCTs) published between January 2007 to May 2016 were identified by searching the Pubmed, EMBASE and Cochrane Library databases. Primary endpoints included operative outcomes (operative time, intraoperative blood loss, number of transfused patients and conversion rates), postoperative outcomes (length of postoperative hospital stay, postoperative morbidity and postoperative in-hospital mortality), and oncologic outcomes (number of harvested lymph nodes, tumor recurrence, disease-free rates and overall survival rates).

Results
17 studies with a total of 1676 patients were included in the review. Compared with open approach, minimally invasive lymphadenectomy demonstrated significant larger number of harvested lymph nodes, longer operative time, lower intraoperative blood loss and shorter postoperative hospital stay. No significant differences were observed between the three groups for the following criteria: lymph-node metastasis, postoperative morbidity, tumor recurrence and postoperative mortality.

Conclusion
Although a technically demanding and time-consuming procedure, minimally invasive lymphadenectomy appears to be safe and feasible and may offer an alternative approach in staging and treatment of cervical cancer. Multicentre randomized controlled trials investigating its long-term oncological outcomes and its cost-effectiveness are required to determine the advantages of this procedure over the open approach in cervical cancer.

Περίληψη

Αντικείμενο: Σκοπός της μελέτης μας ήταν η ανασκόπηση της βιβλιογραφίας όσον αφορά το ρόλο της ελάχιστα επεμβατικής λεμφαδενεκτομής στην θεραπεία του καρκίνου του τραχήλου.

Μέθοδος: Με αναζήτηση στις βάσεις δεδομένων Pubmed, EMBASE, Cochrane Library αναγνωρίσθηκαν μη τυχαιοποιημένες μελέτες (non-RCTs) που δημοσιεύθηκαν μεταξύ Ιανουαρίου 2007 και Μαϊου 2016. Στις βασικές παραμέτρους περιλαμβάνονταν εγχειρητικά αποτελέσματα (χρόνος επέμβασης, διεγχειρητική απώλεια αίματος, αριθμός μεταγγιζόμενων ασθενών και ποσοστά μετατροπής), μετεγχειρητικά αποτελέσματα (διάρκεια νοσηλείας, μετεγειρητική νοσηρότητα και θνητότητα), και ογκολογικά συμπεράσματα (αριθμός λεμφαδένων, υποτροπή νόσου, διάστημα ελεύθερο νόσου και συνολική επιβίωση).

Αποτελέσματα: 17 μη τυχαιοποιημένες μελέτες (non-RCTs) με ένα σύνολο 1676 ασθενών συμπεριελήφθησαν στη μελέτη. Συγκριτικά με τη λαπαροτομία, η ελάχιστα επεμβατική λεμφαδενεκτομή κατέδειξε σημαντικά μεγαλύτερο αριθμό συλλεχθέντων λεμφαδένων, μεγαλύτερο χειρουργικό χρόνο, λιγότερη διεγχειρητική απώλεια αίματος, μικρότερη μετεγχειρητική παραμονή στο νοσοκομείο. Μη στατιστικά σημαστική διαφορά παρατηρήθηκε για τις ακόλουθες παραμέτρους: λεμφαδενικές μεταστάσεις, μετεγχειρητική νοσηρότητα, υποτροπή νόσου και μετεγχειρητική θνητότητα.

Συμπέρασμα: Αν και τεχνικά απαιτητική και χρονοβόρα επέμβαση, η ελάχιστα επεμβατική λεμφαδενεκτομή είναι ασφαλής και εφικτή και μπορεί να αποτελέσει μία εναλλακτική τεχνική στην θεραπεία και σταδιοποίηση του καρκίνου του τραχήλου. Απαιτούνται πολυκεντρικές τυχαιοποιημένες μελέτες για τη διερεύνηση των μακροπρόθεσμων ογκολογικών αποτελεσμάτων και του κόστους της επέμβασης αυτής, ώστε να καθοριστούν τα πλεονεκτήματά της συγκριτικά με την λαπαροτομική προσέγγιση στον καρκίνο του τραχήλου.

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