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Author: Haak, L. van den
Title: Implementing new surgical instruments in minimally invasive surgery
Issue Date: 2018-11-15

Implementing new surgical instruments in minimally invasive surgery

Lukas van den Haak

This PhD thesis was partly funded by the European Regional Development Fund.

Financial support for printing of this thesis was kindly provided by the department of Gynecology of the Leiden University Medical Center, Raad van Bestuur Haaglanden Medisch Centrum, The Nederlandse Vereniging voor Endoscopische Chirurgie (NVEC), Erbe, Chipsoft and the Walaeus bibliotheek.

Titel: Implementing new surgical instruments in minimally invasive surgery
Lukas van den Haak, 2018

ISBN: 978-94-6380-046-4
Lay-out: Ferdinand van Nispen tot Pannerden, *my*-thesis.nl, the Netherlands
Cover design: Ton van Jole
Printed by: ProefschriftMaken || www.proefschriftmaken.nl

Implementing new surgical instruments in minimally invasive surgery

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 15 november 2018
klokke 13.45

door

Lukas van den Haak

geboren te Dongen
in 1979

Promotor	prof. dr. F.W. Jansen
Copromotoren	dr. T.E. Nieboer (Radboud Universitair Medisch Centrum, Nijmegen) dr. J.P. Rhemrev (Haaglanden Medisch Centrum, Den Haag)
Leden promotiecommissie	prof. dr. D. Oepkes prof. dr. drs. M.P. Schijven (Academisch Medisch Centrum, Amsterdam) prof. dr. J.J. van den Dobbelsteen (Technische universiteit, Delft)

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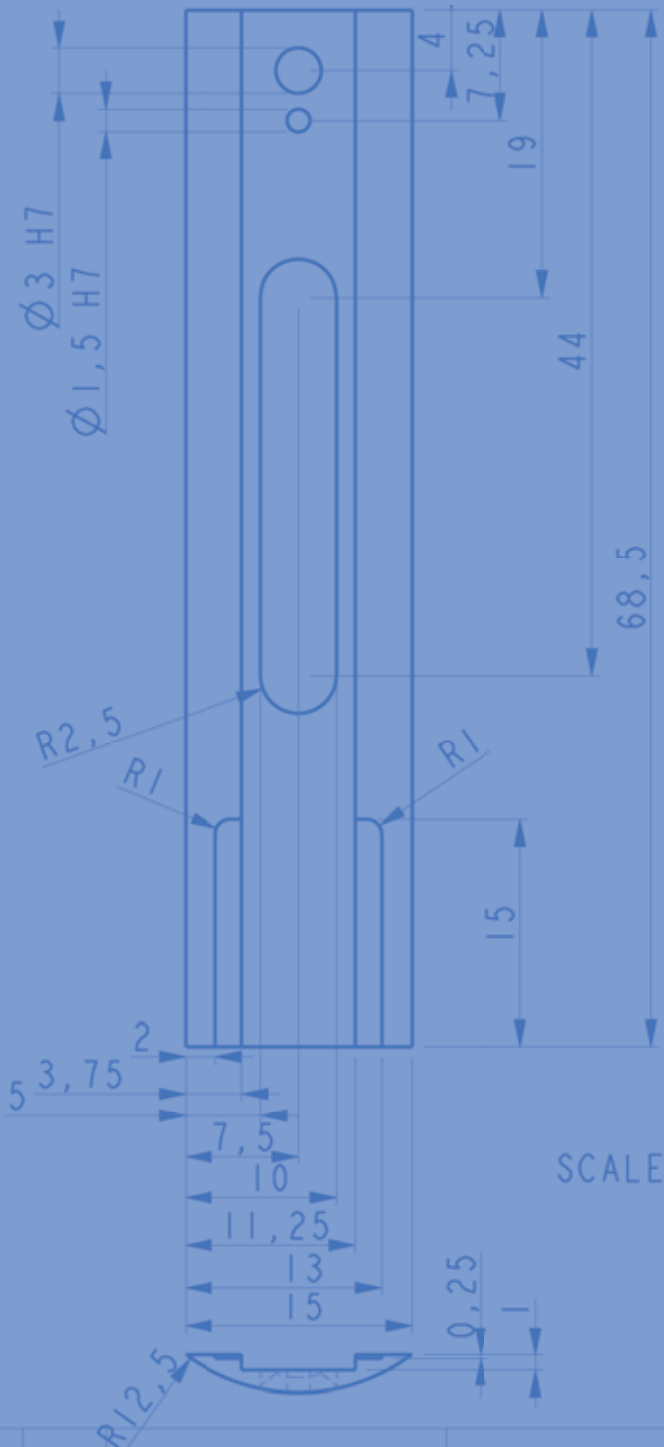
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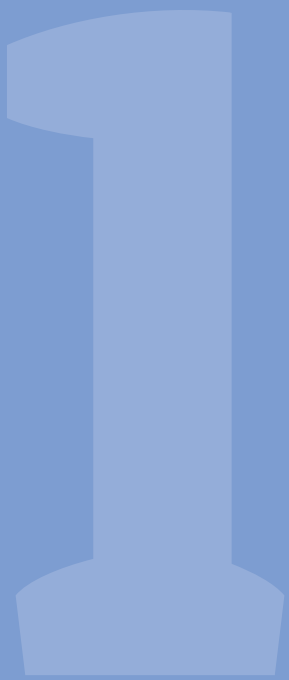
General Introduction



Introduction

Innovations regarding surgical techniques and instruments (henceforth called technology) play a major role in enhancing the efficacy and safety of surgical procedures. Technological developments in the past have enabled a minimally invasive approach to surgical procedures that were previously performed via laparotomy. For instance, the laparoscopic approach is currently the scientific standard in appendectomy, cholecystectomy and hemicolectomy. In gynecology, hysterectomy is increasingly performed via minimally invasive surgery (MIS) and studies have demonstrated that 25% up to 37% of all hysterectomies are currently performed via MIS.[1,2] The importance of the developments leading to MIS was recently acknowledged anew by confirming the advantages of MIS over laparotomy regarding surgical outcomes and patient benefits. [3]

However, since the efficacy and safety of a new technology has usually not been established on a large scale before introduction in the field, innovations may consequently go hand in hand with an impairment of patient safety. Short and long term adverse events have been described after the introduction of new surgical techniques in daily practice. An example of a short term adverse event was the rise in major complications such as major hemorrhage and ureteric injury during the early introduction of laparoscopic hysterectomy (LH).[4] However, these complications could be attributed to learning curve issues. Combined with improvements made in technologies such as electrosurgery, major complications in LH declined and this technique is now considered superior to laparotomy. [5]

And on the other end of the spectrum, adverse events caused by new technology may be only observed long after its introduction in clinical practice. In 2014, 21 years after its introduction in US market, the electromechanical (or *power*) morcellator was discredited. The power morcellator is a surgical device that allows the removal of an enlarged uterus or fibroid via laparoscopic trocars by shredding the tissue into fragments which are small enough to fit through these trocars. However, when reports were published regarding the accidental morcellation of preoperatively undiagnosed uterine sarcoma resulting in a possible upstaging of the malignancy, the U.S. Food and Drug Administration (FDA) decided to discourage the further use of this device. [6]

In this light, the *industry driven approach* to innovations (i.e. coming from medical devices manufacturing companies) and the *clinically driven approach* (based on analyses of problems encountered in daily surgical practice) should be considered. Unequivocally the introduction of the power morcellator has played a role in the successful implementation of the laparoscopic approach to hysterectomy and myomectomy. By manufacturing

more powerful devices, even very large uteri and myoma were eligible for removal via laparoscopy. Yet, an analysis with respect to clinical indications and possible risks of the device was not performed, although early warnings regarding the occurrence of malignant tissue spill were issued in scientific literature.[7-12] The vast majority of all publications regarding power morcellators discussed industry driven specifications such as morcellation speed.[13]

To minimize the chance of unforeseen adverse events, efforts have been made in the past century to regulate the introduction of new technologies. In a research setting human subjects are protected by several medical ethical legal entities, in particular by the 1947 Nuremberg Code, the 1964 Declaration of Helsinki and the 1978 Belmont Report.[14-16] In contrast, in daily surgical practice adaptations and innovations aiming to provide the best care for the individual patient are considered "standard" care. Unfortunately, the distinction between daily surgical practice and research is not always clear. The Belmont report defines daily practice as "*interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success"* and research as "*an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge"*.[16] However it is also stated that "*the fact that a procedure is 'experimental', in the sense of new, untested or different, does not automatically place it in the category of research"*.[16] As a result a grey area exists between daily practice and research, meaning that surgeons may circumvent research regulations by declaring that the innovation is aimed to improve the health of the individual patient. [17,18] Laparoscopic cholecystectomy was introduced in such a fashion. In gynecology, ample experience existed with laparoscopy. In fact, the first laparoscopic appendectomy was performed by a gynecologist.[19] Since the laparoscopic approach to appendectomy was successful and appeared safe, together with the introduction of videoscopy, it was suggested that this approach to cholecystectomy must also be safe. The first laparoscopic cholecystectomy performed in The Netherlands was supervised by a gynecologist since the surgeon was unexperienced with MIS.[20] The laparoscopic route quickly became the new standard in surgery, although comparative trials were lacking. Finally, when larger case series were published it became apparent that complications were significantly higher during laparoscopy due to bile duct lesions.[18,21] Another example is robotic surgery, which quickly became an accepted alternative to routine laparoscopy and open surgery after it was initially introduced in a research setting.[17] In the U.S. alone the number of procedures performed robotically increased by more than 500%, even though convincing evidence preferring robotic surgery over laparoscopy does not exist and learning curve issues as well as patient safety have been questioned.[17]

The bodies responsible for the admittance of new medical devices are the Conformité Européenne (CE) for Europe and the Food and Drug Administration (FDA) for the United States of America. The CE-marking on a product is a declaration of a manufacturer that the device meets the essential requirements of European health, safety and environmental protection legislation.[22] However it is important to realise that the CE mark does not evaluate or guarantee the clinical safety of a device. The FDA has two objectives: providing the public reasonable assurances of safe and effective de- vices while avoiding overregulation of the industry.[23] A premarket approval process was installed for new devices in which the safety and effectiveness for the devices intended use has to be demonstrated by standard scientific methods.[23] However, the FDA has been criticized for its methods. Firstly, to avoid overregulation an alternative for the premarket approval process was installed, called the 510(k) provision (named after section 510(k) of the Food, Drug and Cosmetic Act). It states that new versions of existing (and deemed safe) devices are exempt from the premarket approval process. In the meantime, the criteria for the 510(k) provision were broadened, which has resulted in an increase of new medical devices on the market that were not extensively tested for their safety and effectiveness. For example, approval of the radiofrequency ablation of liver tumors was granted merely by proving that this technique could actually ablate liver tissue. However, no evidence existed regarding the clinical efficacy of this treatment compared to standard treatment at that time.[21] Moreover, it was shown that the majority of devices that were withdrawn from the market due to safety issues, were FDA approved based on the 510(k) provision.[23] Secondly, the FDA does not regulate the manner in which a device is used in daily clinical practice, meaning that devices may be used off-label without FDA surveillance.[17]

In the Netherlands, the shortcomings of current regulations regarding the introduction of new technology were also acknowledged. In 2014, a cooperation between *de Orde van Medisch Specialisten, het Zorginstituut Nederland,* and *het Kennisinstituut van Medisch Specialisten*, resulted in a guideline called *Leidraad Nieuwe Interventies in de Klinische Praktijk* (NIKP).[24] This guideline aims to structure the introduction of new technology in health care interventions (such as surgery) to better warrant patient safety. Interestingly, emphasis is put on the preclinical stage of the development of new technology, before it is applied in human subjects. In general, 5 stages are considered in surgical innovation, yet only the very first stage *(stage 0)* concerns in-vitro tests. [18] (table 1) In all other stages the new technology is applied in human subjects. The Dutch guideline provides methods that can be applied in this first stage when evidence regarding safety and efficacy does not yet exist.

Table 1: 5 stages of surgical innovation

Stage		Title	Setting
0		Innovation	Pre-human
1		Innovation	In human
2	a	Development	In human
	b	Early dispersion and exploration	In human
3		Assessment	In human
4		Long-term implementation and monitoring	In human

With this in mind this thesis was initiated to explore a range of possible assessment methods, including those suggested by the NIKP, that can be used in stage 0 of surgical innovation. Using LH as a starting point, two medical devices acted as a template for the assessments used in this thesis. To begin, the NIKP guideline was applied to the technical development of a new prototype for a uterine manipulator that is designed to facilitate the manipulation of the uterus and its separation from the vagina during LH. Next, the controversies regarding the use of a power morcellator were addressed. This device is currently a highlight in minimally invasive gynecological research topics. With the new design of the manipulator and the morcellator in mind, several studies were undertaken combining a clinical and technical point of view. The main objective of this thesis is to assess different methods and tools that are available in stage 0 of surgical innovations. It was hypothesized that ideally, major hazards to patient safety can be identified before new technology is introduced in daily surgical practice.

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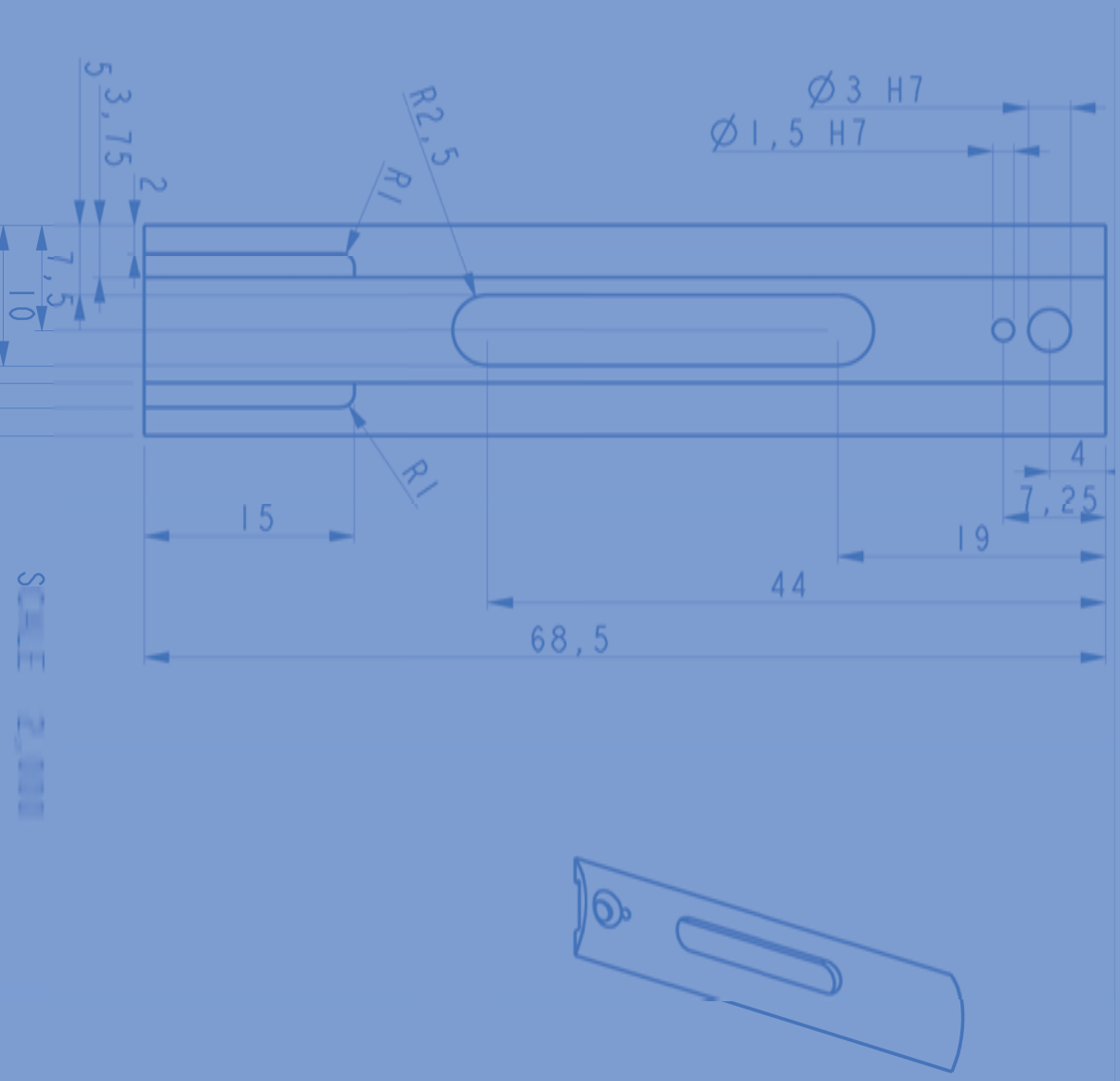

SCALE 2:1

A new approach to simplify surgical colpotomy in laparoscopic hysterectomy

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Gynecol Surg. 2016;13:63-69

Abstract

New surgical techniques and technology have simplified laparoscopic hysterectomy and have enhanced the safety of this procedure. However, the surgical colpotomy step has not been addressed. This study evaluates the surgical colpotomy step in laparoscopic hysterectomy with respect to difficulty and duration. Furthermore, it proposes an alternative route that may simplify this step in laparoscopic hysterectomy. A structured interview, a prospective cohort study and a problem analysis were performed regarding experienced difficulty and duration of surgical colpotomy in laparoscopic hysterectomy. Sixteen experts in minimally invasive gynecologic surgery from 12 hospitals participated in the structured interview using a 5-point Likert Scale. The colpotomy in LH received highest scores for complexity (2.8 ± 1.2), compared to AH and VH. Colpotomy in LH was estimated as more difficult than in AH (2.8 vs 1.4, $p < .001$). In the cohort study, 107 patients undergoing LH were included. 16% of the total procedure time was spent on colpotomy (SD 7.8%). BMI was positively correlated with colpotomy time, even after correcting for longer operation time. No relation was found between colpotomy time and blood loss or uterine weight. The surgical colpotomy step in laparoscopic hysterectomy should be simplified as this study demonstrates that it is time consuming and is considered to be more difficult than in other hysterectomy procedures. A vaginal approach to the colpotomy is proposed to achieve this simplification.

Introduction

New surgical techniques and technical equipment have attempted to facilitate laparoscopic hysterectomy (LH), after shortcomings of LH in comparison with vaginal hysterectomy (VH) and abdominal hysterectomy (AH) were demonstrated.[1] New alternatives for conventional suturing, such as bipolar coagulation, have improved hemostasis of the uterine and ovarian pedicles.[1] Furthermore, in a systematic review the superiority of vessel sealing devices with respect to blood loss and shorter operation time in some abdominal procedures was demonstrated compared to other electrothermical devices.[2] Finally, barbed sutures have been introduced for vaginal vault closing and this technique appears to be equal compared to standard sutures with respect to time to cuff closing, cuff healing and sexual function.[3] Although some of these effects are debatable, for instance due to possible contributing factors such as learning curve, they do demonstrate the efforts to facilitate the LH. Certainly, notwithstanding the well-known benefits of LH, VH remains the gold standard for the hysterectomy procedure [1,4], even though in contrast with this statement recent studies have shown that LH was associated with shorter hospital stay, less blood loss and less postoperative pain compared to VH.[5,6] Yet, LH is still associated with a longer operating time.[4,7] Furthermore, previous studies have demonstrated that LH is regarded as more difficult when compared to AH and VH.[8] Learning curve issues and implementation errors have contributed to these results. However, there still are technical opportunities to simplify the LH procedure. Our hypothesis is that the colpotomy should be addressed in this context. Colpotomy is part of the final surgical steps in the LH procedure, following the ligation of the uterine arteries, the skeletonizing of the cervix and the dissection of the bladder from the cervix. These steps are relatively hazardous and time consuming in the procedure. It is in this anatomical area where most of the bleeding and ureter injuries occur.[9,10] Moreover, the delicacy of laparoscopic surgery in this anatomical area was demonstrated by the initial higher incidence of ureter injuries during LH, which only decreased after a certain learning curve was passed.[11] In this light, an alternative route for colpotomy has been investigated: analysis of the current colpotomy procedure demonstrated that the main difficulties of this surgical step are the limited visibility during colpotomy (due to the anterior view of the endoscope combined with the location of the cervix deep in the pelvis), and the need for a 360° circular cutting motion during colpotomy. To overcome these difficulties, a vaginal approach to the colpotomy was suggested. A first test with a prototype of a vaginal colpotomy device on an in vitro vaginal model demonstrated a significant reduction of colpotomy time. [12]

The aim of this study was to substantiate our hypothesis and to further evaluate the possibilities of a vaginal approach to colpotomy. The experienced difficulty, the duration of the surgical colpotomy step, and possible agents of change are evaluated. In addition,

the idea of a vaginal approach to colpotomy is shaped into a new surgical instrument that may simplify colpotomy. [13]

Materials & Methods

Firstly, to investigate the difficulty of the colpotomy procedure, a structured interview was performed among experts in minimally invasive gynecologic surgery working at different hospitals throughout the Netherlands. The interview assessed the participants perception regarding the surgical step of the colpotomy. Furthermore, they were asked about their opinion regarding several features of the proposed facilitation of the colpotomy. (Figure 1) Participants were asked to answer using a 5 point Likert scale: 1 meaning 'easy' / 'not important' , to 5 meaning 'complex' / 'important'.

Next, a prospective cohort study was performed at 2 hospitals specialized in minimally invasive gynecologic surgery. From June 2010 till May 2014, LH procedures were timed to assess the duration of colpotomy. The total operating time (TOT) was defined as the time from the insertion of the Veress needle to the final stitches used for closing last trocar incision site. Colpotomy time (CT) was defined as the time from the first incision in the vaginal fornix (after ligating the uterine arteries and all uterine ligaments) until the

1. What is your estimation of the total procedure time of a total hysterectomy and what is the estimated time required for the separation of the uterus from the vagina (absolute time and relative to the total procedure time)?
2. Can your estimate the complexity of separating the uterus from the vaginal wall for the different procedures?
3. How important is it to maintain the possibility to manipulate the possibility to manipulate the uterus with a manipulator while dissecting the uterus?
4. What is the importance of coagulation when separating the uterus from the vaginal wall with respect to the following items: Easy cutting, less bleeding, impaired wound healing, accurate dissection, less collateral tissue damage.
5. How important is a visual position mark of the dissection device in a uterus extraction product such that the position of the instrument in the vagina can be seen through the laparoscopic endoscope?
6. What effort will it take to adapt the surgical procedure in your hospital and implement the use of this instrument?
7. All in all, do you think the envisioned instrument may provide a benefit enabling a faster and/or easier uterus extraction?

Fig. 1 Structured interview

complete separation of the cervix from the vaginal wall. An extrafascial technique was used to perform total laparoscopic hysterectomy. The vaginal wall was opened anteriorly at the vesicovaginal fold, after which the colpotomy was completed. All consecutive LH procedures were eligible for inclusion. This study was exempt from approval by the Medical Ethics Committee. Procedures were performed by 5 gynecologists who perform LH on a regular basis and have experience in well over 100 TLH procedures. The number of participating gynecologists was chosen to enhance the external validity of the outcome. Inter-surgeon variability was minimised by using similar surgical procedure protocols. Furthermore, all surgeons received their training at the Leiden Residency Program. The Valtchev or Clermont Ferrand uterine manipulator were used. Bipolar and ultrasonic instruments were used for colpotomy. Basic patient characteristics were gathered. The uterine weight and the total amount of blood loss were measured in the operating room. Patients were excluded in case of missing colpotomy time. Complications were classified according to the severity of the complications on the basis of the framework set by the Dutch Society for Obstetrics and Gynecology (NVOG).[14]

Statistical analysis

Baseline characteristics were summarized by means and standard deviations and, when applicable, by numbers and percentages. For the structured interview, an independent sample t- test and a paired t-test were used to compare experts versus residents and the type of hysterectomy respectively. For the prospective study, t tests were used when applicable. A Pearson's correlation coefficient and Analysis of Variance (ANOVA) techniques were used to test any correlation between different variables and colpotomy. A generalized linear model was performed to assess the independent effect of certain parameters (such as uterine weight, Body Mass Index (BMI)) on the duration of colpotomy. All tests were performed at the .05 level of significance. SPSS 20 was used to analyze all data.

Results

Structured interview

Sixteen experts from 12 hospitals were interviewed. (Tables 1 and 2) On average, the experts performed 35 (SD 24) hysterectomy procedures annually, of which 59 % (SD 24) LH procedures, 19% (SD 21) VH and 22% (SD 15) AH. The estimated TOT 114 (SD 24) minutes, and they estimated to spent 18% (SD 11) the TOT on the colpotomy. The colpotomy in LH received highest scores for difficulty (2.8 ± 1.2), compared to AH and VH. Colpotomy in LH was estimated as more difficult than in AH (2.8 vs 1.4, $p < .001$). The same trend is seen for the difficulty of colpotomy in LH versus VH (2.8 vs 2.0), however this difference was nog significant ($p = .08$). With respect to the vaginal approach to simplify colpotomy, the following functions of the envisaged instrument

Table 1: Participants opinion regarding colpotomy (N=16 expert)

	Mean (SD)	p value
Number of hysterectomy procedures per year	35 (24)	
Amount of TLH (%)	59 (24)	
Amount of VH (%)	19 (21)	
Amount of AH (%)	22 (15)	
Estimated length of TLH procedure (minutes)	114 (24)	
Estimated colpotomy time TLH (minutes)	20 (10)	
Complexity of colpotomy TLH [a]	2.8 (1.2)	
Complexity of colpotomy VH [a]	2.0 (1.3)	
Complexity of colpotomy AH [a]	1,4 (.6)	
Estimated colpotomy vs total OR time (%)	18 (11)	
TLH vs VH	2.8 vs 2.0	.08
TLH vs AH	2.8 vs 1.4	< .001
VH vs AH	2.0 vs 1.4	.02

TLH: total laparoscopic hysterectomy, *VH* vaginal hysterectomy, *AH* abdominal hysterectomy vaginal hysterectomy

[a]1 easy–5 complex

Table 2: Preferred functions and adaptation of the new device (N=16)

	Mean	SD
Importance of a uterine manipulator 4.5 1.4	4.5	1.4
The Importance of coagulation instead of cutting when separating the uterus from the vagina		
- Collateral tissue damage	2.3	1.6
- Easy cutting	3.5	2.0
- Wound healing	2.6	1.6
- Accurate dissection	3.1	2.2
- Bleeding	4.2	1.1
Importance of markings so that a vaginal instrument is visible during laparoscopy	4.6	0.7

Scale 1–5 = not–moderate–important

were regarded as moderately important to important by the participants: the ability to manipulate the uterus (4.5, SD 1.4), the presence of coagulation to stop bleeding during the colpotomy procedure (4.2, SD 1.1) and the existence of markings on the device to help visualize the device by the camera (4.6, SD .7).

Table 3: Patient characteristics and procedure data (N=107; 91 Leiden University Medical Center and 16 Bronovo hospital)

		Mean	SD	P value
Age (years)		49.4	10.6	
BMI (kg/m²)		27.4	7.0	
Parity [a]		2	1.4	
		Number (%)		
Previous operations	None	66 (62)		
	One or more abdominal surgeries	41 (38)		
Indication for operation	Abnormal bleeding and / or uterine leiomyoma	68 (64)		
	(pre-)malignancy	37 (35)		
	Other [b]	2 (2)		
Total operating time (min)		116.4	35.3	
Colpotomy time (min)		17.9	7.8	
TOT minus CT (min)		98.5	31.5	
Uterine weight (g)		242.8	175.0	
Estimated blood loss (ml)		142.5	194.7	
Complications (total and %)	Peri-operative lesions [c]	1 (1%)		
	Post-operative infection [d]	6 (6%)		
	Other [e]	9 (9%)		
Colpotomy-total OR time (%)		16	5	
Colpotomy time	No complications occurred (n=91)	18.0	8.1	
	A complication occurred (n=15)	17.9	6.0	1.0
Colpotomy time	No previous abdominal surgery	17.6	7.3	.6
	With previous abdominal surgery	18.4	8.6	

BMI body mass index

[a] = median

[b] = 1 endometritis and salpingitis, 1 abdominal pain

[c] = 1 bladder injury

[d] = 5 urinary tract infections, 1 pneumonia

[e] = 1 ileus, 1 urinary retention, 1 re-admittance for unexplained fever, 1 lost needle during surgery resulting in enlargement of the trocar incision,1 patient with facial subcutaneous emphysema that required admittance at the intensive care unit,1 infected hematoma, 1 vaginal cuff dehiscence occurring 4 weeks after surgery, 1 abdominal pain that led to additional surgery 10 days after TLH resulting in a partial oophorectomy and 1 repeat laparoscopy on the same day regarding a loss of blood exceeding 300ml.

Table 4 Pearson correlation and generalized linear model (N=107; 91 LUMC and 16 Bronovo)

		Colpotomy time (min)		
	Pearson correlation		Sig.	N
BMI (kg/m²)		.329	.001	104
Age (years)		.278	.004	107
TOT minus CT (min)		.380	.000	105
Uterine weight (g)		.092	.349	105
Estimated blood loss (ml)		.082	.399	107
	Generalized linear model	B[a]		
BMI (kg/m2)		.403	<.001	
Uterine weight (g)		-.002	.703	

BMI body mass index

[a] B unstandardized regression coefficient

Colpotomy analysis

Out of 164 consecutive patients, 107 patients undergoing LH were included. 57 (35%) were excluded due to missing colpotomy time. Patient characteristics and procedure data are shown in Table 3. Most common indications for surgery were abnormal bleeding and/or uterine myoma. The mean total operating time was 116.4 minutes (SD 35.3 min) and the mean colpotomy time was 17.9 minutes (SD 7.8 min). On average, 16% of the total procedure time was spent on colpotomy. BMI was positively correlated with colpotomy time (.320 and .311, both p=.001), and the generalized linear model confirmed the identified correlation and proved that it was independent from the other variables (Table 4). No statistically significant correlation was found between colpotomy time and uterine weight or blood loss.

Discussion

This study demonstrates that the surgical colpotomy is a time consuming step in the LH procedure, that is preceded by the hazardous dissection of the uterine arteries, bladder and cervix, risking blood loss and ureter injuries. Colpotomy time comprises 16% of the total operation time, even reaching 45%. Albeit an extreme value, it does demonstrate the difficulty that can be experienced when performing this task. This is substantiated by our structured interview. In accordance with a previous study[8], our structured interview revealed that experts find colpotomy in LH significantly more difficult than in AH, and that the same trend is seen for colpotomy in LH compared to VH (although not significant). It is also demonstrated that a rise in BMI proved to be associated with a longer colpotomy time. The effect of BMI on the duration of surgery is in line with other

studies.[15,16] However, in our study the effect of BMI on the colpotomy time remained even after correcting for total operation time. Apparently, higher BMI apart from the additional procedure time, accounts for an additional complicating factor regarding the colpotomy step. These women especially may benefit from the simplification of this procedure. Moreover, as the incidence of obesity is increasing, higher BMI will become part of everyday work in laparoscopic surgery.[17] No other factors, such as the amount of blood loss, previous abdominal surgery or the presence of complications seemed to influence the duration of colpotomy. Surprisingly, also for uterine weight no correlation was found with colpotomy time. It is our opinion, that the colpotomy procedure can be regarded as independent from "uterine" factors, such as uterine weight. Indeed, when performing the colpotomy after all uterine ligaments and arteries have been dissected, the obtained additional mobility of the uterus will compensate for restrictions due to uterine weight. However, although uteri weighing up to 930 grams were removed, the vast majority of uteri in our cohort weighed below 360 grams. Therefore we realize that, based on the results from our cohort, our statement may not fully apply to very large uteri. Yet support of our opinion can be found in literature, where the feasibility of LH in women with larger uteri has already been established.[18,19] A limitation of our study is the high number of exclusions, especially given the prospective design of this study. However, the overall effect of the exclusions on the outcome of our study is limited. Missing data can be considered random and therefore effect cohort size rather than the results, although the introduction of bias cannot be fully excluded. Only one surgical protocol was used for our prospective study and this raises the question of external validity regarding other surgical protocols. However the relative colpotomy time that resulted from our prospective study matches the estimated relative colpotomy time from our interview (16% vs 18% respectively), in which gynecologists participated who use different protocols. This study did not focus on procedural steps of the LH other than colpotomy, which could be considered a flaw. For instance, dissection and sealing of the uterine artery would have been an interesting addition. On the other hand, this step has already been enhanced by new surgical techniques and technology. All other steps of the hysterectomy procedure are relatively straightforward and appear to be in no apparent need of improvement. Notwithstanding these shortcomings, our findings regarding colpotomy time are important. A recent study demonstrated that operative time was an independent predictor of postoperative morbidity and reoperation.[20] Furthermore, a cost analysis of different approaches to hysterectomy showed that patient operation room costs and total patient costs are higher for LH when compared to VH, and that longer operation time proved to be an important contributor to these higher costs. [21] In light of these studies, reducing CT and thereby the TOT may have beneficial effects on patient morbidity as well as on health care costs. This will become increasingly important, since there is an increase of laparoscopic hysterectomy procedures at the expense of the number of vaginal hysterectomies [22]

Vaginal approach for colpotomy

A prototype for a vaginal colptomizer device has been assembled.[13] Although several methods exist to perform the surgical colpotomy such as bipolar and harmonics, to our knowledge, the vaginal route to colpotomy has not yet been proposed. Figure 2 demonstrates our prototype.

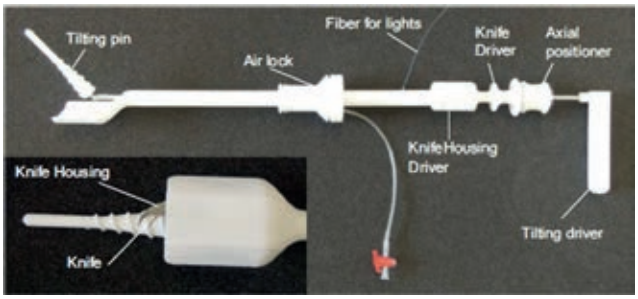

Fig. 2: MobiSep prototype

The intrauterine part of the manipulator has mobility in all planes (i.e. anterior-posterior, lateral and rotation). After introducing the manipulator into the uterus, a cap is positioned over the cervix. This cervical cap, which rotates, has several functions: it presents the vaginal cuff and helps to push the uterus cranially. Furthermore, it houses the knife that enables the vaginal colpotomy. The knife is deployed and operated by moving the knife driver and the handle of the manipulator. The exact location where the knife is introduced into the vaginal wall (and hence in the abdominal cavity) is identified by a light source in the manipulator. Figure 3 and 4 demonstrate the knife during colpotomy in a human cadaver test and in detail respectively.

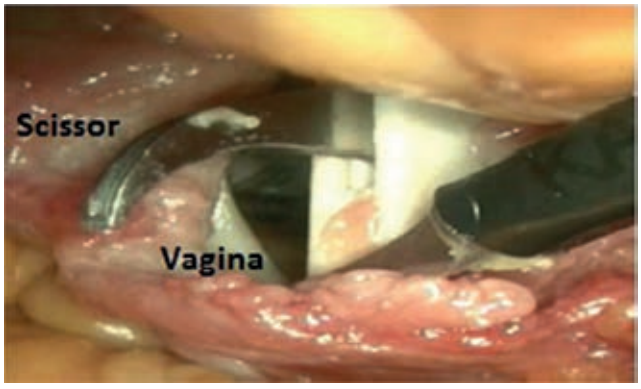

Fig. 3: Vaginal colpotomy with MobiSep prototype in human cadaver test

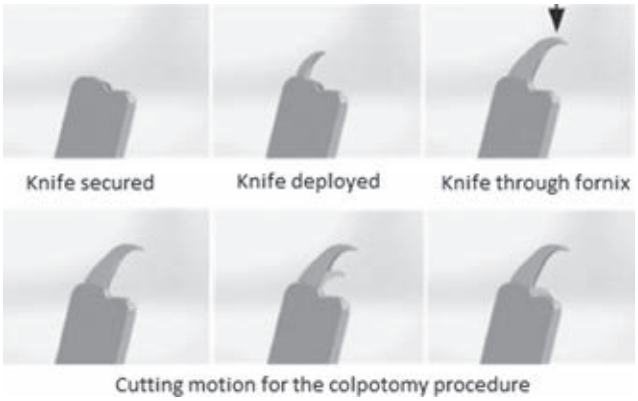

Fig. 4: Detail of the knife action of the vaginal colpotomizer in relation to safety cap

Finally, after colpotomy is completed, the entire surgical specimen and the manipulator are removed. Certain questions remain to be answered. For instance, our interview tried to assess the preference for a coagulation based or "cold knife" based cutting mechanism. Coagulation was preferred in case of bleeding and , to lesser extent, to facilitate the cutting action. However, some concerns were raised over the possible negative effects of coagulation with respect to wound healing. Several studies have reported a higher incidence of vaginal vault dehiscence after LH when compared to VH and AH. [23-25] It has been suggested that electrocoagulation may be the cause for this higher incidence, due to more extensive tissue damage and/or suboptimal tissue healing.[26,27] However, in large series no effect of electrocoagulation was demonstrated with respect to the occurrence of vaginal vault dehiscence. [28] Moreover, no effect of the power settings was observed. [28] It was concluded that the current available scientific evidence does not support one technique over the other, and it is expected that this topic will continue to be a main point of interest for gynecological societies. However, in light of the feasibility of the device, a cold knife cutting mechanism was designed. The structured interview also demonstrated the need for a manipulator function integrated in the device. The importance of a uterine manipulator during LH has been demonstrated in literature. A manipulator is considered to increase the distance between the ureter and uterine arteries, thereby creating more space for the dissection of the uterine arteries.[29] Furthermore, in a recent Delphi study, full agreement was reached regarding the use of a uterine manipulator during LH to prevent ureter injuries during LH.[30] This resulted in the final design of the prototype: a uterine manipulator with an integrated vaginal colpotomizer.

In all, the significance of the present study is the clinically driven approach to innovating the difficult surgical colpotomy step. Experiences in the past have shown the need for a careful introduction of new technology in daily practice.[31,32] Consequently, innovation should start with a thorough analysis of the problem at hand. The eVALuate

study has taught us that LH has certain disadvantages with respect to patient safety when compared to VH and AH.[1] Technical developments have already contributed to the enhanced safety of LH. However further simplifying the LH is necessary, since our study demonstrates that the surgical colpotomy step takes place in an anatomical area which is at risk for complications, is regarded as difficult, and comprises a considerable amount of the total duration of the LH procedure. Therefore, much can be gained by simplifying this step .

Conclusions

Earlier studies have taught us that LH has certain disadvantages with respect to patient safety when compared to VH and AH. Technical developments have already contributed to the enhanced safety of LH. However further simplifying the LH is necessary, since reducing the operation time of LH may reduce health care costs and complication rates. [20,21]Our study demonstrates that the colpotomy step in LH should be simplified. Not only is this surgical step time consuming, it is also regarded as significantly more difficult when compared to AH. A vaginal approach of the colpotomy step may solve these issues. A surgical instrument was designed as a uterine manipulator with an integrated vaginal colpotomizer. The device intends to address the shortcomings of the current colpotomy technique. Clinical studies will commence shortly to evaluate the efficacy and safety of the vaginal approach to colpotomy.

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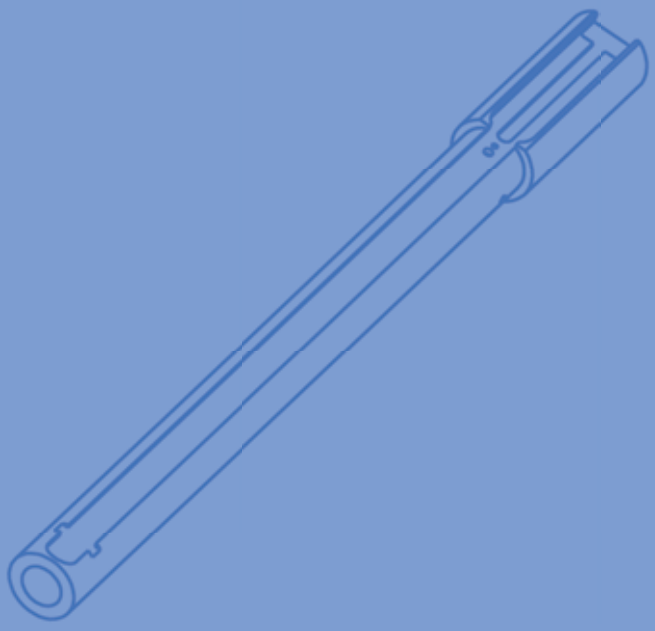

Efficacy and Safety of Uterine Manipulators in Laparoscopic Surgery: a Review

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Arch Gynecol Obstet. 2015 Nov;292(5): 1003-11

Abstract

Purpose: This review aims to objectively assess the efficacy and safety of uterine manipulators as reported in scientific literature. Furthermore it evaluates as to which manipulator best suits which surgical procedure.

Methods: PubMed, Embase, Web of Science, COCHRANE, CINAHL, Academic Search Premier, ScienceDirect and the MAUDE database were searched. Technical information was retrieved from the manufacturers.

Results: 25 articles covering 10 uterine manipulators were found. Studies regarding implementation and use of manipulators are scarce, only 2 surveys were found comparing different manipulators. Moreover, clinical evidence proving the efficacy of manipulators with respect to prevention of complications, inherent to laparoscopic surgery, does not exist.

Conclusion: the use of uterine manipulators is well established and it is clear that uterine manipulators offer the easiest way to handle the uterus during surgery. However, detailed information regarding efficacy and safety is scarce. Clinical evidence substantiating the assumed mechanism of prevention of ureter injuries was not found. Our review did not find the optimal manipulator. Some are more versatile than others and not all instruments are appropriate for all types of surgery. Therefore, gynecologists should choose the manipulator that best suits the type of surgery that is performed.

Introduction

Uterine manipulators are widely adapted surgical instruments that facilitate various surgical procedures. In gynecology, the importance of a uterine manipulator regarding the prevention of ureter injuries during laparoscopic hysterectomy (LH), has been highlighted.[1] This reduced risk with respect to ureter injury is reported in several studies.[1-6] According to these publications, this may be achieved in several ways. Firstly by lateralising the uterus, manipulators facilitate a perpendicular dissection of the uterine artery. Secondly they elevate the uterus exposing the cul-de-sac, especially important in case of endometriosis. Thirdly uterine manipulators provide delineation of the vaginal fornices, necessary for colpotomy and maintain the pneumoperitoneum after the vagina is incised. Finally manipulators increase the distance between the cervix and ureter by pushing the uterus cephalad, thus allowing safer dissection around the cervix. Meanwhile, it remains questionable if these advantages have been well researched. Although several surveys are available that offer an overview of different manipulators and their capabilities, they do not address the efficacy and patient safety of the different manipulators.[7,8] Since the indications for laparoscopy in gynecology are expanding, manipulators are likely to be found more often in the operation room and in different procedures. Without an objective overview, making an informed decision when introducing a uterine manipulator in daily surgical practice will be difficult. To obtain the necessary information, a literature review to gather all published data regarding existing manipulators and their mode of action was performed. These data were combined with an overview of reported adverse effects during the use of a uterine manipulator. With this review we aim to objectively assess the efficacy of uterine manipulators as reported in scientific literature and to evaluate as to which manipulators best suit which surgical procedure.

Materials & Methods

A review of literature was performed, searching PubMed, Embase, Web of Science, COCHRANE, CINAHL, Academic Search Premier and ScienceDirect. Our search strategy was finalised by the research librarian of the medical library at the Leiden University Medical Centre (LUMC). The following terms were used: hysterectomy (MeSH), colpohysterectomy, (gyn(a)ecologic) surgical procedures (MeSH), uterus (MeSH), uteri, colon (MeSH), colectomy (MeSH), sigmoid (MeSH), sigmoidectomy, uterine diseases (MeSH), mobilizer, mobiliser, manipulator. This review focusses on all manipulators suitable for (total) laparoscopic hysterectomy ((T)LH), since these instruments are most versatile. Manipulators frequently used in clinical practice were added to the search strategy. Reports on the manipulators were also searched with “Google”. We

crosschecked the reference lists of retrieved articles for relevant studies. Articles were selected by LH and CA, with FWJ acting as third reviewer in case of disagreement. All full text articles, with uterine manipulators and their actions as main subject, were included. Articles not focussing on the actions of a manipulator were excluded. Articles describing manipulators and the possible spread of malignant cells were also excluded. Although this is a very important topic, it reaches beyond the bounds of what we intended to evaluate. When only an abstract was available we contacted the author for a complete copy of the article. We contacted the manufacturer for further details in case the company's website provided insufficient information. Qualifications on manipulators as used by original authors were adapted in this review.

Finally, the Manufacturer and User Facility Device Experience (MAUDE) database was checked for all reported complications over the last 10 years. This database is a passive surveillance system of the FDA for medical device safety. This study was exempt from approval by the Medical Ethics Committee.

Results

299 references and 1 article from an online journal were found, of which 263 references were excluded based on title or content of the abstract and 6 due to missing full text versions (Figure 1).

Of the remaining 32 references LH and CA disagreed on the inclusion of 9 titles. Of these 9, 7 titles were excluded after assessment by FWJ. These articles did not sufficiently focus on uterine manipulators or its actions. Finally, a total of 26 references and the article from the online journal covering 10 manipulators suitable for (T)LH were evaluated in our review (Table 1).[1-26] The Hourcabie, a frequently mentioned manipulator, could not be assessed since no information regarding its manufacturer was found. The Koninckx manipulator, Donnez manipulator, McCarus Volker Fornisee System and Secufix Uterus Manipulator were also not described in this review since no scientific publications were available on these instruments.

For purpose of accessibility, the literature is presented according to the manipulator. Table 2 offers an overview of the manipulators and their characteristics. It is largely based on the only 2 existing surveys that evaluated and compared different uterine manipulators.[7,8] Table 3 states all reports in the MAUDE database.

The Hohl manipulator is a reusable instrument. It has a 130˚ range of motion in the anterior-posterior plane. Lateral movement and elevation are given to be good and

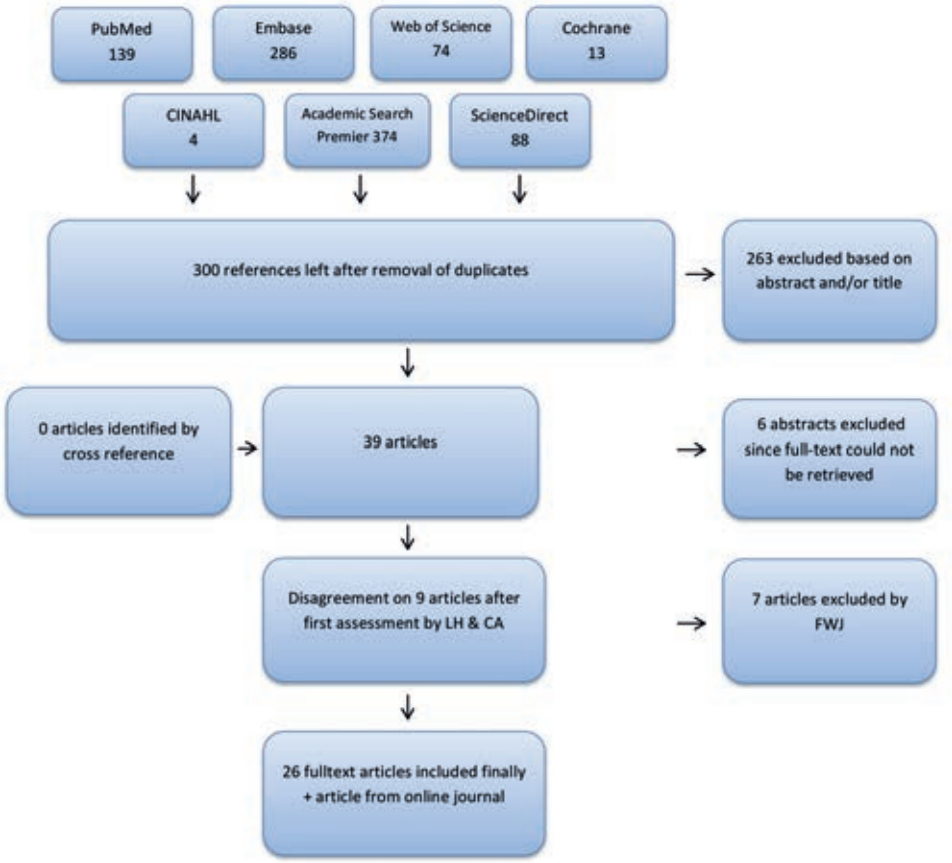

Figure 1: Flow diagram of study selection

handling is reported to be easy. However, assembly is stated as difficult.[7] Most publications were found regarding this manipulator: three prospective studies, one retrospective study, a product survey and one case report.[4,7,12-16] One retrospective and one prospective cohort study were perfomed by Mueller *et al.*, including 44 and 567 patients respectively.[4,14] 1 ureter injury, 4 bladder injuries and 1 vagina injury occurred. In an additional prospective study, the Hohl manipulator was compared in women with BMI < 30 (219 patients) versus BMI >30 (38 patients).[13] 1 ureter injury, 1 bladder and 1 vaginal injury were observed, all in the group with BMI < 30. However, there was a significant difference in uterine weight with smaller uteri in the group with BMI>30 (246 vs 185g). Another prospective cohort was published of 1432 patients undergoing total intrafascial laparoscopic hysterectomy (TAIL) using a Hohl manipulator, experiencing 1 ureter and 8 bladder injuries.[15] Finally, a case report exists describing a uterine perforation and bowel perforation in a patient were a Hohl manipulator was used. [12] No reports on this manipulator were found in the MAUDE database.

Table 1: Review of Literature

Manipulator	Publication	Type	Subject	No. of patients	Complications / injuries
Hohl	Mueller 2005	Retrospective cohort	TLH with Hohl	44	None
	Mueller 2010	Prospective Controlled	BMI <30 vs BMI>30	219 vs 38	1 ureter 1 bladder 1 vagina [b]
	Mueller 2012	Prospective cohort	TLH with Hohl	567	1 ureter 4 bladder 1 vagina
	Hohl 2010	Prospective cohort	TAIL vs AH vs VH [a]	1432 TAIL	1 ureter 8 bladder
	Janssen 2013	Retrospective case analysis	Ureter injuries		
	Akdemir 2014	Case report	Complication Hohl	1	Uterine rupture and bowel penetration
	Mettler 2006	Product review	Survey manipulators		
Clermont Ferrand	Janssen 2013	Retrospective case analysis	Ureter injuries		
	Mettler 2006	Product review	Survey manipulators		
Clearview	Sharp 1995	Randomised trial	Clearview vs Cohen cannula	25 vs 25	2x perforated uterus during dilation of the cervix
	Mettler 2006	Product review	Survey manipulators		
RUMI I + KOH	Keriakos 2000	Prospective cohort	TLH with RUMI + KOH	25	none
	Ng 2007	Retrospective cohort	TLH with RUMI + KOH	435	Ureter 0.2 % Bladder 0.2 %
	Ng 2007	Retrospective cohort	TLH with RUMI + KOH	512	Ureter 0.2% Bladder 0.4% Vagina 1%
	Koh 1998	Product review	TLH with RUMI + KOH		
	Wu 2005	Case Report	Complication RUMI	2	Uterine rupture

Table 1: Continued

Manipulator	Publication	Type	Subject	No. of patients	Complications / injuries
	Ellett 2013	Case Report	Complication RUMI	1	KOH cup left behind
	Mettler 2006	Product review	Survey manipulators		
Vcare	Greenberg 2009	Product Review	Vcare		
	Mettler 2006	Product review	Survey manipulators		
	Janssen 2013	Retrospective case analysis	Ureter injuries		
Mangeshikar	Mettler 2006	Product review	Survey manipulators		
Vectec	Tamburro 2011	Prospective cohort	Effect suction on endometrium	10	
McCartney Tube	McCartney 2004	Retrospective cohort	TLH + McCartney	1500	
	McCartney 1995	Retrospective cohort	TLH + McCartney	73	
	Jansen 2013	Retrospective case analysis	Ureter injuries		
	Elkington 2006	Review	TLH		
Valtchev	Reich 1994	Product review	Surgical instruments for laparoscopy		
	Bernstein 1995	Product review	Valtchev		

[a] TAIL: Total Intrafascial Laparoscopic Hysterectomy; AH: abdominal hysterectomy, VH: vaginal hysterectomy; TLH: total laparoscopic hysterectomy

[b] all injuries occurring in pts with BMI < 30.

Table 2: Uterine Manipulators [7,8,13,14,17,19-25]

		Range of motion			Characteristics						Use	
		Ant-post	Lat[a]	Elevation	Type	Traumatic	Reusable	Delineation	Pneumoperitoneum	Handling	Assembly	Suitable	Less Suitable
Hohl		130	+++	++	screw	Yes	Yes	++	++	+++	+	(T)LH	Endometrioses of the cul-de-sac
Clermont Ferrand		140	+++	+++	screw	Yes	Yes	+++	+++	+++	+	(T)LH, endometriosis of cul-de-sac	Cervical preservation, due to dilation to Hegar nr. 9
Clearview		210	+++	++	balloon	Yes	No	-	-	+++	+++	All procedures except (T) LH, including chromopertubation	(T)LH
RUMI System[b]		140	+++	+	Balloon	Yes	Partly	+++	+++	++	+	Alround, (T)LH	Endometrioses in the cul-de-sac, narrow vagina
RUMI II system[b]		140	+++	?	balloon	Yes	Partly	Yes	Yes	++	++	Insufficient information	
Vcare		*na*	++	++	balloon	?	No	+++	+++	+++	+++	(T)LH, alround	Large / heavy uteri

Table 2: Continued

		Range of motion			Characteristics						Use	
		Ant-post	Lat[a]	Elevation	Type	Traumatic	Reusable	Delineation	Pneumoperitoneum	Handling	Assembly	Suitable	Less Suitable
Dr Mangeshikar[c]		?	+++	+++	Tenaculum	Yes	Yes	+++	+++	+++	+++	(T)LH, endometriosis of cul-de-sac	
Vectec		*na*	?	?	Suction / screw	No	No	Yes	yes	?	?	Insufficient information	
McCartney tube		-	-	-	-	No	No	+++	++	+++	*na*	(T)LH	Other gynaecological procedures
Valtchev		135	?	?	Tenaculum	Yes	Yes	Yes	Yes	+++	+++	alround	

Table based on available data in publications and from manufacturers.

+++ good, ++ moderate, + poor, - does not support, na: not applicable, ?: not found

na: not applicable; (T)LH: (Total) Laparoscopic Hysterectomy

[a] Not independent movement, except for Mangeshikar manipulator

[b] RUMI system consists of the RUMI manipulator, the Koh cervical cup, and the Koh colpo-pneumo-occluder.

[c] Also offers independent laevo- and dextrorotation

Table 3: Complications caused by uterine manipulators based on MAUDE database and literature

Manipulator	Event	Measures needed?
Hohl	Uterine rupture and bowel penetration	Laparotomy for bowel repair
Clearview	Parts of the manipulator left behind in patient	
	Disintegration of manipulator while inside patient	Removal with hysteroscopy
	Uterine perforation due to cervical dilation	
RUMI I	Laceration of vaginal wall (multiple reports)	Suturing.
	Excess haemorrhage from laceration	Blood transfusion
	Parts of the manipulator left behind in patient (multiple reports)	
	Disintegration when removing the manipulator	
	Spontaneous release of cup during colpotomy	Prolonged operation time to check integrity of ureters
	Retroperitoneal haematoma caused by uterine perforation after hyperinflation of the intra-uterine balloon	Laparotomy and uterine artery ligation
	Vaginal mucosa stuck in RUMI	
Vcare	Disintegration when removing the manipulator	
	Parts of the manipulator left behind (multiple reports)	
	Laceration of vaginal wall (multiple reports)	Suturing
	Perforation of vagina and cervix due to cup	
	Perforation of uterus with intra-uterine tip	
	Repetitive Strain Injury of the assistant	
	Melting of the cup	

The Clermont Ferrand manipulator is a reusable instrument and offers 140˚ range of motion in the anterior-posterior plane. Lateral motion and elevation are mentioned to be good and handling is easy.[7] No studies evaluated the efficacy of this instrument and no reports in the MAUDE database exist.

The Clearview manipulator is a lightweight disposable instrument. With 210˚, it has the greatest range of motion in the anterior-posterior plane of all the manipulators. It was previously known as the Endopath uterine manipulator. It is reported to have excellent characteristics.[7] Unfortunately it does not offer delineation of the vaginal fornices and it cannot maintain the pneumoperitoneum, making it less suitable for total laparoscopic hysterectomy (TLH). It allows the manipulation of the uterus by the gynecologic surgeon, without the need of an assistant holding the manipulator. This manipulator is the only instrument to have been tested in a randomised trial.[17] In this trial, 50 patients were

randomly assigned to a Clearview manipulator or a Cohen cannula. Various laparoscopic procedures were performed except for (T)LH. The authors found a better range of motion (120˚ versus 84˚ p<0.0001 anterior, -20˚ vs -8˚ p<0.0001 posterior) in favour of the Clearview manipulator. However, the Clearview took longer to insert (116s vs 27s, p=.02). No significant differences were found in other parameters, such as ease of use. Two minor complications occurred in the group of the Clearview manipulator: in both cases a cervical perforation occurred during dilation because of cervical stenosis. Two reports were found in the MAUDE database, concerning one case where the manipulator disintegrated inside the patient and one case where parts of the manipulator came loose and remained inside a patient.

The RUMI system consists of the RUMI manipulator, the Koh cervical cup and the Koh colpo-pneumo-occluder. It has a 140˚ range in the anterior-posterior plane. Along with the Hohl manipulator, most publications were found on this instrument: two retrospective and one prospective studies, two case reports and several product reviews.[2,3,5-7,18,26] However, the two retrospective cohort studies, including 435 and 512 patients, describe the same patient population, with one containing more patients due to a longer inclusion period. [5,6] Injury rate in the largest cohort was 0.2% for ureter, 0.4% for bladder and 1% for the vagina. The prospective study describes a cohort of 25 patients.[2] Two case reports exist: the first is a uterine rupture in 2 patients due to hyperinflation of the intra-uterine balloon of the RUMI manipulator, and the second a KOH cup that remained inside a patient and was discovered 14 months after surgery. [18,26] Lastly, several reports were found in the MAUDE database on the disintegration of the instrument or on parts being left behind, in some cases leading to lacerations of the vaginal wall. The RUMI system has been updated, however no studies were found on the RUMI II system.

The Vcare manipulator is a lightweight disposable instrument. It does not offer independent motion of the intra-uterine tip, rather it uses leverage to manipulate the uterus. The Vcare has a wide range of motion, it is said to offer good delineation and to maintain the pneumoperitoneum well. Also, handling is easy. However the lightweight design is reported to be less suitable to manipulate larger uteri.[7,8,19] Multiple reports were found in the MAUDE database on disintegration of the instrument or on parts being left behind. Also lacerations of the vaginal wall have been described. Lastly, the melting of the cervical cup was mentioned in one report, however without causing harm or damage to the patient.

The Dr. Mangeshikar manipulator is the only instrument to offer indepent laevo- and dextrorotation of the intra-uterine tip. It offers a wide range of motion in all directions and assembly and handling are mentioned to be easy.[7] Unfortunately, no additional publications are available on this instrument.

The Vectec manipulator, like the Vcare, uses levarage to manipulate the uterus instead of a intra-uterine tip with independent movement. It is a disposable instrument. One study was found, demonstrating that the suction mechanism by which the manipulator secures itself, does not modify the endometrium and therefore should be safe to use.[20] The Vectec is also available with a screw mechanism.

The Valtchev manipulator is one of the oldest instruments in our study. It is a reusable instrument and offers 135˚ movement in the anterior-posterior plane. It is reported to be easy to assemble and handle.[7,25] The McCartney tube was also included in this review. Strictly speaking it is not an intra-uterine manipulator as it does not have an intra-uterine section, therefore not allowing movement of the uterus in a frontal or horizontal plane. It does, however, offer delineation of the vaginal fornices and is able to maintain the pneumoperitoneum well. It also allows the introduction of materials through the vaginal tube instead of the transabdominal trocars. Since it provides excellent cephalad movement of the uterus, it has a place among the uterine manipulators as will be discussed later. Two retrospective cohorts (73 and 1500 patients) describe the McCartney tube as manipulator.[21,22] Regrettably, no reports on ureter injuries are made in these cohorts. No reports were found in the MAUDE database.

Discussion

This review offers an overview of all scientific literature on manipulators. There is a paucity of well-designed studies that assess the different instruments. Only one randomised trial exists and it addressed the Clearview manipulator.[17] Based on our review, the Clermont Ferrand, Dr. Mangeshikar, Valtchev and RUMI System manipulators seem to be most versatile due to excellent capabilities, although the Clermont Ferrand and RUMI System are considered difficult to assemble. The Vcare, Clearview and Valtchev are very user friendly. However, the Vcare is considered too light to use in larger uteri. The Clearview manipulator lacks a cervical cup and cannot maintain the pneumoperitoneum, making it less suitable for TLH; however it may be a useful instrument for other gynecological procedures. The Dr. Mangeshikar manipulator is the only instrument in our review to provide independent laevo- and dextrorotation of the uterus, thereby presenting the uterine arteries without having to stretch the manipulator too far laterally. In theory, this may offer an advantage especially in case of vaginal atrophy or stenosis. The Clermont Ferrand and the Dr. Mangeshikar offer the best exposure of the cul-de-sac due to excellent uterine elevation. In case of endometrioses of the cul-de-sac, these 2 instruments may be the instrument of choice.

Surprisingly, little evidence exists regarding the efficacy and safety of uterine manipulators. Furthermore, although many authors feel that the cephalad motion of the uterus is extremely important for avoiding urinary tract injuries, since this increases the distance between ureter and cervix [3-5], no study exists demonstrating the actual mechanism of the increased distance between cervix and ureter by pushing the uterus cephalad. Only one study mentioned having visualised an increased distance between ureter and cervix when using the RUMI system by placing lighted ureteral stents. [3] However, the author did not explain how this was performed nor did he supply figures of his observations. The same author also states that distance between ureter and cervix actually decreased when using a cervical cup that is too large. If indeed true, this finding is worrisome, since it implies a reduction of patient safety when using an improper cervical cup. Moreover, no studies are available on this specific subject, making it impossible to predict the correct shape of the cervical cup, including cups of existing manipulators. In addition, several articles were found where this movement is provided by alternative methods. [9-11]

Considering the low incidence of ureter injuries, it will be difficult to demonstrate the effect of a uterine manipulator as ultimate tool for the prevention of these injuries. Moreover, ureter injury rate depends on far more than just the use of a uterine manipulator, such as learning curve and experience of the gynecologist, and the presence of additional disease, e.g. endometriosis. Subsequently, although the earlier mentioned Delphi study by Janssen *et al* is the best evidence we have regarding the prevention of ureter injuries, it is important to realize that the recommendations on ureter injuries were established based on expert opinions rather than clinical evidence. [1] This is substantiated by the analyses of 31 ureter injuries performed by the same author.[16] A uterine manipulator was used in the vast majority (83.9%) of cases of ureter injury. These results affirm that a uterine manipulator is not the ultimate tool to prevent ureter injuries.

Unfortunately, statements regarding the safety of the reviewed manipulators cannot be made. Since there certainly is under-reporting of complications, accurately determining a rate of complications caused by a uterine manipulator is impossible. However, a trend is seen that (partly) disposable, relatively lightweight uterine manipulators that need assembly are at risk for adverse events due to disintegration of the instrument or to parts being left behind in patients.

A cost analysis of the manipulators could not be performed, due to variable prices between countries, sometimes even between hospitals. Given this variability and since we compare (partly) disposable manipulators to reusable ones, we feel a full cost analysis is unlikely to add significant data to our review.

Although our search did not include the possible effects of manipulators on uterine malignancies, this topic should be addressed since laparoscopy is increasingly implemented in gynecologic oncology. In both cervical and endometrial malignancies, clinic-pathological parameters such as infiltration depth and lymphovascular space invasion (LVSI) may be influenced when a manipulator is used [27-31] However, it is hypothesised that other factors such as artefacts and tissue handling contributed to these findings. More importantly, no negative effects on the oncological outcome were found in these studies. In addition, larger studies including a prospective randomised trial did not find this influence on clinic-pathological parameters. [32-36] Based on these studies it can be concluded that the use of a uterine manipulator during gynecologic oncology procedures is unlikely to negatively affect a patients oncological outcome. However, in absence of definitive evidence, several authors suggest closing the fallopian tubes via cautery or clipping prior to the insertion of a manipulator to prevent spread of malignant cells into the abdomen.

The shortcoming of our study is the limited number of unbiased papers and randomised trials available on this subject. Since the aim of our study was an objective evaluation of the existing literature, we did not test the instruments ourselves. This makes an extensive evaluation of the manipulators more difficult. As a result, all characteristics of the manipulators are based mostly on the 2 available surveys. Furthermore, strong conclusions with respect to complications during the use of certain manipulators cannot be made due to earlier mentioned reasons.

However, to our knowledge, this review is the first review to independently assess manipulators based on available studies and on safety reports. In contrast with some studies we've found, our study is not commercially driven. Therefore, it offers valuable additional information to existing literature. Furthermore, our finding that statements with respect to the prevention of ureter injuries are not substantiated by clinical evidence has important implications. Given the possible adverse effects, our study demonstrates that a uterine manipulator should not be introduced without fair consideration. Ideally, for every procedure, the most appropriate manipulator should be considered.

Conclusion

Uterine manipulators are very useful instruments that help expose the anatomy during surgical procedures. However, evidence regarding their efficacy and safety is scarce. Although uterine manipulators are probably the easiest way to handle the uterus during laparoscopy, alternatives without manipulators have been published. More importantly, evidence proving how manipulators prevent ureter injuries is absent. The findings of

1 study, mentioning a decrease in distance between cervix and ureter when using too large cervical cups, are worrisome and in need of further investigation.[3] Subsequently it is unclear if uterine manipulators are the ultimate tool to prevent ureter injuries.

Conclusions with respect to reported complications caused by uterine manipulators cannot be made, due to underreporting. However, it appears that lightweight disposable manipulators in need of assembly seem to be at risk to cause specific adverse effects. Therefore they should be used with extra care.

Our literature review did not provide the ultimate uterine manipulator. The Clermont Ferrand and Dr. Mangeshikar manipulator seem to be the most versatile, and the latter is the only manipulator in our review to offer independent laevo- and dextrorotation. However, no publications such as cohort studies or randomised trials exist on these instruments. In all, gynecologists should choose the uterine manipulator that best meets the requirements for the type of surgery to be performed.

Acknowledgements:

We would like to thank J.W. Schoones for his contribution to our search strategy. (J.W. Schoones is the Information Specialist at the Walaeus Library of the Leiden University Medical Centre. J.W. Schoones has no conflict of interests to declare.)

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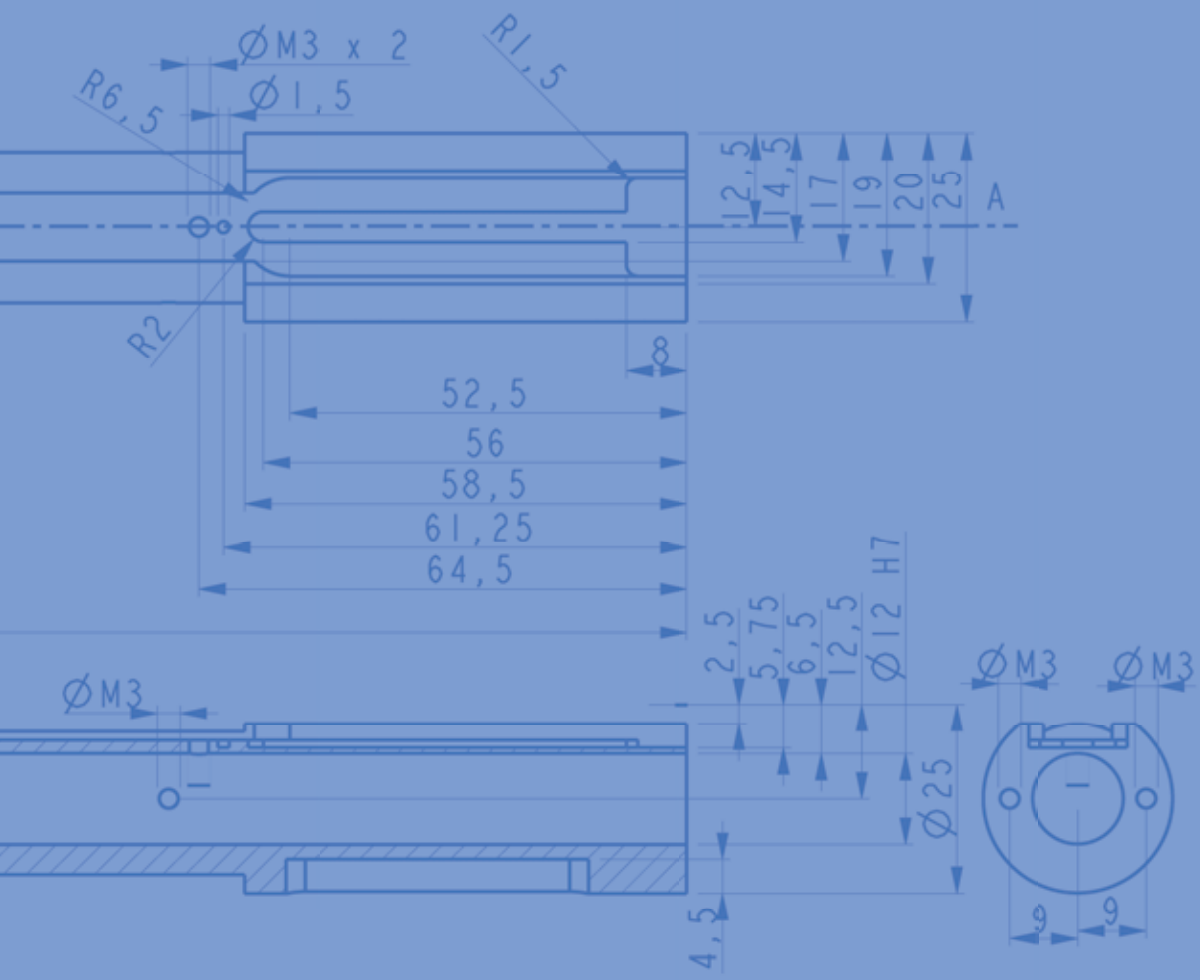
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Human cadavers to evaluate prototypes of minimally invasive surgical instruments: a feasibility study

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Technol Health Care. 2017 Dec 4;25(6):1139-1146

Abstract

Background: New technology should be extensively tested before it is tried on patients. Unfortunately representative models are lacking. In theory, fresh frozen human cadavers are excellent models.

Objective: To identify strengths and weaknesses of fresh frozen human cadavers as research models for new technology prior to implementation in gynecological surgery.

Methods: During pre-clinical validation studies regarding the MobiSep uterine manipulator, test procedures were performed on fresh frozen cadavers. Both the experimental setup as the performance of the prototype were assessed.

Results: Five tests including six human cadavers were performed. Major changes were made to the MobiSep prototype design. The cadavers of two tests closely resembled surgical experiences as found in live patients. The anatomy of 4 of the 6 cadavers was not fully representative due to atrophy of the internal genitalia caused by age and due to the presence of pathology such extensive tumorous tissue.

Conclusion: The cadaver tests provided vital information regarding design and functionality, that failed to emerge during the in-vitro testing. However, experiments are subject to anatomical uncertainties or restrictions. Consequently, the suitability of a cadaver should be carefully assessed before it is used for testing new technology.

Introduction

Innovations in surgical instruments and techniques (hereafter called 'technology') are important tools to enhance patient safety in minimally invasive surgery (MIS). They facilitate technically challenging procedures, which constitute MIS. At the same time, experiences in the past have demonstrated the risks that accompany the implementation of such innovations. For instance, the introduction of laparoscopic cholecystectomy resulted in a significant increase of the number of bile duct injuries. In gynecology, prolapse repair surgery using vaginal meshes, Essure sterilization and the use of power morcellators in laparoscopic hysterectomy or myomectomy, are examples of widely used technology that have recently come under scrutiny due to unforeseen adverse effects. [1-4] To reduce the risk of these adverse effects, pre-market approval for new technology by a Conformité Européenne (CE) mark or review by the U.S. Food and Drug Administration (FDA) is required in Europe and the USA respectively.[5] However approval or clearance does not guarantee safety, and even minor changes or additions to an existing technology, which undergo less extensive evaluation, may be hazardous.[6] At present, there are 5 stages in the implementation of new technology into early daily practice [7]: innovation (stage 0), testing of proof of concept and safety (stage 1), development and exploration (stage 2a-b), assessment (stage 3) and long term implementation and monitoring (stage 4). As soon as stage 1, testing is performed on live humans. It is only in stage 0 that the pre-human tests take place. Evidently, compared to the introduction of new pharmaceuticals, which is bound by vigorous protocols, new technology is subject to less strict implementation criteria. This has recently been recognised by the European Parliament (EP). In May 2016, the EP reached a provisional agreement on more strict rules for new technology. In addition, the importance of pre-human stage 0 testing has been incorporated in recent guidelines regarding the introduction of new technology, created by clinicians.[8] These guidelines strongly advise the surgeon to familiarize him- or herself with the new technology by practicing on appropriate training models, before it is implemented in daily practice.[8] However, finding a proper model is difficult. For instance in gynecology, animal models are generally not representative due to different anatomy of the internal genitalia. In addition, virtual reality tools have difficulty depicting real life conditions including tactile feedback.

In theory, human cadavers could be of value in establishing the feasibility and safety of a new product. They are widely used in universities to demonstrate anatomy to medical students. Furthermore, human cadavers have been proposed for the laparoscopic training of residents.[9,10] However, no evidence is available on the use of human cadavers for testing new technology. The aim of our study is to evaluate the strengths and shortcomings of human cadavers as a model for testing new technology in minimally invasive surgery, during the pre-clinical stage of development.

Materials & Methods

Fresh frozen cadavers were used to maximally approach conditions as found in live patients, such as tissue resistance and tissue colour. On arrival at the anatomy department, the cadaver is cooled at -40°Celsius, after which it is stored at -20°C. Before use, the cadaver is defrosted and after use it is stored again at -20°C. It is possible to use the cadaver up to 3 times with this protocol.

To assess the feasibility of fresh frozen cadavers as a model during preclinical testing, the mode of action of a new instrument, the MobiSep uterus manipulator and separator, was tested during a total laparoscopic hysterectomy (TLH) as part of the pre-clinical development stage. The MobiSep instrument consists of a uterine manipulator and a vaginal blade that allows a vaginal approach to colpotomy during hysterectomy (figure 1) .[11-13]

All procedures were performed according to a strict study protocol. The following parameters were rated poor, moderate, sufficient or excellent: accessibility of the vagina, visualisation of the cervix, ease of cervical dilatation, insertion of the manipulator into the cervix, insertion of the intra-uterine tip into the uterus, the ease of manipulation of the uterus and of colpotomy. Furthermore, adverse tissue effects were registered. Standard instruments for MIS were used. The degree of possible manipulation of the uterus was verified by using an existing uterine manipulator (model Vectec®), before the MobiSep instrument was tested.

Experiments were performed at the anatomical laboratories of the University Medical Centre of Utrecht and the Radboud University Medical Centre, Nijmegen. FWJ, JPR and TEN performed all tests. Approval was obtained from the Department of Anatomy of the participating institutes.

Results

Five tests including 6 fresh frozen human cadavers were performed, the results are presented in table 1.

The first hysterectomy was performed abdominally to familiarize the research team with the MobiSep instrument, all other procedures were performed via standard multiport abdominal laparoscopy. The first test was performed using the original MobiSep prototype (figure 1). This device comprises an intra-uterine tip and cervical cup which are attached to a rotational mechanism responsible for uterine manipulation. The

Table 1: test results

		Accessibility of the vagina	Visualisation of the cervix	Cervical dilatation	Insertion of manipulator	Positioning the intra-uterine tip	manipulation	colpotomy	Main instrument adjustments
Test 1		Good	good	poor [a]	Poor [a]	Poor [a]	Excellent	Not performed	Reducing maximal manipulation
Test 2		Moderate	Moderate	Poor [a]	Poor [a]	Poor [a]	Excellent	Not performed	Replacing rotation with DEAM. Independent movement of cervical cup
Test 3		Moderate	Moderate	Moderate	Moderate	Good	Excellent	Poor	Removal of colpotomy function
	Cadaver 1[b]	Moderate	Poor	n/a	n/a	n/a	n/a	n/a	n/a
Test 4	Cadaver 2 [b]	Good	Good	Moderate	Moderate	n/a	n/a	n/a	n/a
Test 5		Good	Good	Good	Good	Good	Good[c]	n/a	Strengthening DEAM

[a] Due to severe atrophy of the internal genitalia

[b] Test 4 could not be performed fully due to the apparent absence of cervix and uterus in one case, and due to a malignancy occupying the small pelvis in the second case.

[c] After cutting uterine ligaments

n/a: not applicable

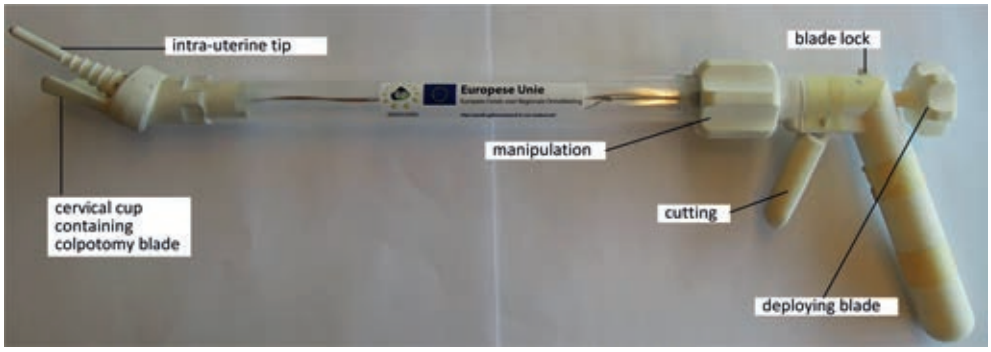

Fig. 1: MobiSep

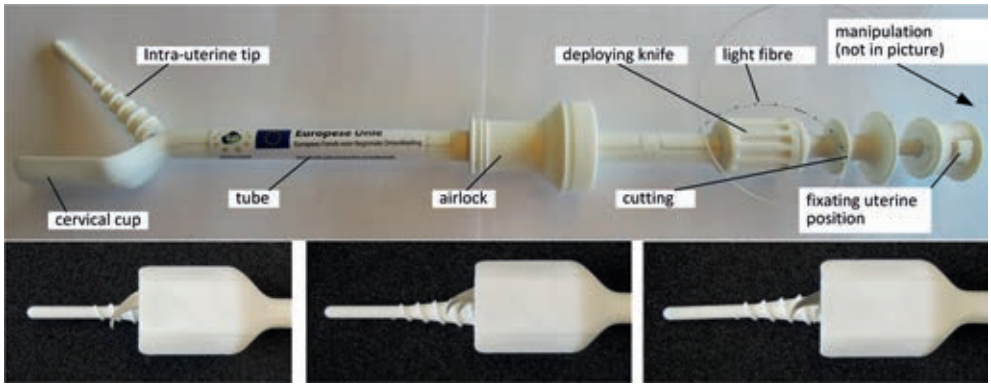

Fig. 2: MobiSep

blade to perform colpotomy is located inside the cervical cup. Manipulation up to 90° anteriorly and laterally was demonstrated with MobiSep. However, the extreme range of motion combined with the size of the rotational unit, caused extensive tissue damage, to the point of tearing the uterus from the vaginal wall. Furthermore, due to the design, manipulation posteriorly was not possible.

Based on these results, the prototype was adapted for the second test. The maximum anterior motion was reduced to 60°, and posterior manipulation was added. Furthermore the cogwheel of the rotational unit was encased to prevent tissue damage. Manipulation to the maximum ability of the instrument was feasible. Unfortunately, extensive tissue damage occurred again, this time due to the fixated cervical cup which did not allow adapting to the present anatomy. It was concluded that to avoid tissue damage, the cervical cup and rotational unit should operate separate from each other. However due to the nature of the design, this functionality could not be incorporated into the device. Therefore, the MobiSep instrument was redesigned. The rotational unit was replaced by a

multi-directional intra-uterine tip based on the DEAM mechanism.[14] This mechanism consists of an easy steerable tip and was inspired by the tentacles of a squid. In addition, the new prototype enables independent movement of the cervical cup encasing the colpotomy blade. (figure 2) This blade was first evaluated in test 3. Two issues were found. Firstly, it proved difficult to bring the tissue under sufficient tension with the cervical cup, and to perform the colpotomy in the desired tissue plane and direction. Additional handling of the tissue by the surgeon or the assistant via laparoscopy was needed. Secondly, it was concluded that a thermal or ultrasonic cutting device is preferred over a cold-knife. Due to the complexity of such a system, it was decided to develop a uterine manipulator without separator based on the DEAM system and, parallel to this process, to evaluate the feasibility of a thermal or ultrasonic blade. Test 4 was scheduled to assess the strength of the DEAM system, as originally, this system was developed for endovascular procedures. Although 2 cadavers were available, unfortunately test 4 could not be performed due to anatomical abnormalities of the cadavers. Therefore, a 5th test was organized. Manipulation before the main ligaments of the uterus were dissected proved difficult due to lack of strength of the DEAM system. However, after dissection and before colpotomy, uterine manipulation was excellent in any direction without restrictions. It was the conclusion that the DEAM mechanism has excellent potential as a uterine manipulator, however the strength of this mechanism needs to be further enhanced.

Discussion

The present study describes our experiences with human cadavers as a model for testing the feasibility and safety of new technology in a pre-clinical stage of development. Several strengths of the model were found. The mode of action of the MobiSep device was extensively tested on in-vitro models, where the functionality of all features was established including the rotational mechanism and the vaginal colpotomy blade. Nevertheless, the cadaver tests provided vital information regarding design and functionality of the MobiSep prototype, that failed to emerge during the in-vitro testing. This resulted in a substantial alteration of the MobiSep design and function. The rotational device was removed and replaced by an alternative mechanism, the cervical cup was redesigned to move independently, and the colpotomy blade is further developed before additional testing. Apparently, there is a big gap between results obtained from in-vitro situations versus real life ones. Therefore, it can be concluded that human cadavers as a model offer a valuable contribution in the pre-clinical stage of the development of new technology.

These findings are in agreement with multiple studies demonstrating the benefits of using human cadavers for surgical training purposes. [15-17] Moreover, cadavers as a

laparoscopic training model were preferred over high-fidelity virtual reality simulators. [18] Fresh frozen cadavers were favoured in most studies, although other preservation methods may closely mimic tissue appearance and handling of fresh frozen specimens. [17,19] Interestingly, studies on the value of human cadavers in the developmental stages of new technology were not found.

Our tests also revealed several limitations of the human cadaver model. Only 2 cadavers were regarded as an optimal model (test 3 and 5). The cervix and uterus of the cadavers used in test 1 and 2 were severely atrophied. Cervical dilatation and insertion of the instrument was difficult, even with the standard manipulator. This could have negatively influenced tissue handling and manipulation, which complicates the interpretation of the test results. Test 4 could not be performed altogether, even though 2 cadavers were available. In the first cadaver, a cervix and uterus could hardly be identified, possibly due to a congenital abnormality. The second cadaver apparently suffered from a malignant process spreading throughout the small pelvis. As a result, the bladder, uterus and intestines were incorporated in this process and fixed to the pelvic wall. Therefore, identification of the pelvic organs was not possible and manipulation could not be evaluated.

These limitations could possibly be overcome if more information on the cadaver is available. Privacy legislation however, prohibits the disclosure of the cadavers' full medical history. In addition, the actual anatomy can only be assessed after the cadaver has already been prepared for the test. Finally, not all institutes may have sufficient suitable fresh frozen specimens at their disposal, making it difficult to implement this model on a wider scale.

In addition to this limitations, a critical evaluation is fair from an ethical point of view, regarding the necessity of using human cadavers for testing new technology. In our opinion, the acquired knowledge regarding the mechanism of vaginal colpotomy by the device could only have come from the human cadaver model due to its specific anatomy. Moreover, testing high risk, new technology on cadavers before it is introduced in live patients can easily be justified. However, the results from our study show that a thorough preparation is necessary to select a suitable cadaver for the intended test. Furthermore, considerations in the early stage of development regarding basic design and mode of action, such as instrument dimensions in our case, should ideally be evaluated in proper non-human models. In this light, the ongoing developments in 3D printing are of interest. Recent papers have studied the value of 3D models for training purposes, and the feasibility of creating representative models of human anatomy has been demonstrated. [20-22] These models of human anatomy may prove valuable in the future.

Finally it is important to realise that a cadaver test is one component of the developmental and implementation stage of new technology. In order to minimize the chance of direct or long-term adverse events occurring, several other measurements should be taken. For instance, a prospective risk inventory (PRI) may be attempted, to identify and correct all possible adverse effects before new technology is introduced. [23] In addition, post-market surveillance to register all complications should be centralised and be mandatory.

In all, human cadavers provide important insights of new technology during the pre-clinical developmental stage, before the new technology is tested in live patients for the first time. A thorough preparation to select a suitable cadaver to match the intended test is necessary. This will prevent the improper use of human remains and will ensure that hazards that may be overlooked in non-human models become apparent before tests in live patients.

Acknowledgments

We are indebted to the people who donated their remains to science, and to their families. We would like to thank the employees of both participating Departments of Anatomy for their cooperation.

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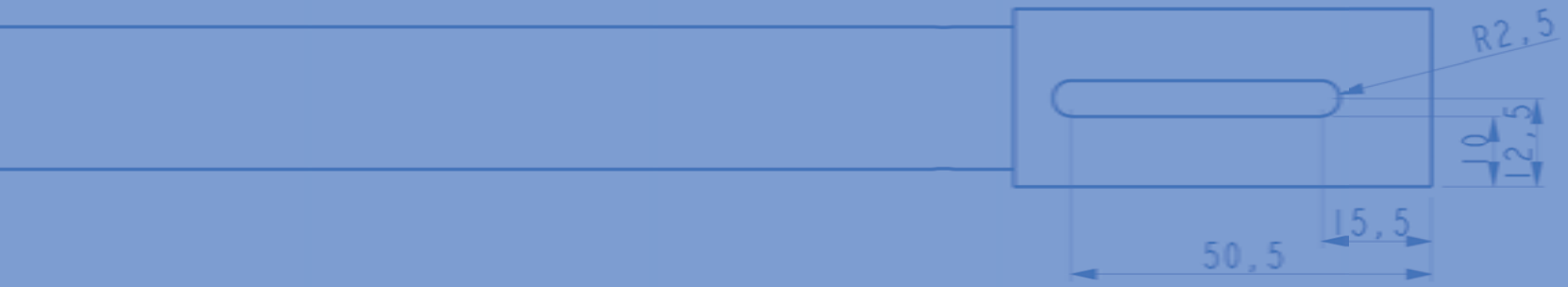
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Assessing basic 'Physiology' of the Morcellation Process and Tissue Spread: A Time Action Analysis

L. van den Haak, E. A. Arkenbout, S. R. C. Driessen, A. L. Thurkow, F. W. Jansen

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J Minim Invasive Gynecol. 2015 Feb;22(2):255-60

Abstract

Study Objective: To assess the basic morcellation process in laparoscopic supracervical hysterectomy (LSH). Proper understanding of this process may help enhance future efficacy of morcellation regarding prevention of tissue scatter.

Design: Time Action Analysis was performed based on video imaging of the procedures (Canadian Task Force classification II-2)

Setting: Procedures were performed at Leiden University Medical Centre (LUMC) and St. Lucas Andreas Hospital (SLAZ), Amsterdam.

Patients: Women undergoing LSH for benign conditions.

Interventions: Power morcellation of uterine tissue.

Measurements and Main Results: The morcellation process was divided into 4 stages: tissue manipulation, tissue cutting, tissue depositing and cleaning. Stages were timed and perioperative data were gathered. Data were analysed as a whole, and after subdivision into three groups according to uterine weight: <350g, 350-750g, >750g. A cut-off point was found at uterine weight of 350g, after which an increase in uterine weight did not affect the cleaning stage. Tissue strip cutting time was used as a measure for tissue strip length. With progression of the morcellation process, the tissue strip cutting time decreases. The majority of cutting time is of short duration, 60% of the cutting lasts 5 seconds or less, and these occur later on in the morcellation process.

Conclusion: With the current power morcellators, the amount of tissue spread peaks and is independent of uterine weight after a certain cut-off point (in this study 350g). There is a relative inefficiency in the rotational mechanism because mostly small tissue strips are created. These small tissue strips occur increasingly later on in the procedure. Because small tissue strips are inherently more prone to scatter by the rotational mechanism of the morcellator, the risk of tissue spread is highest at the end of the morcellation procedure. This means that LSH and laparoscopic myomectomy procedures may be at higher risk for tissue scatter than TLH. Finally, engineers should evaluate how to create only large tissue strips or assess alternatives to the rotational mechanism.

Introduction

Morcellation has allowed laparoscopic surgeons to remove large uteri and myoma, thereby offering more women the benefits of a minimally invasive approach to their surgery. Yet the United States Food and Drug Administration (FDA) has recently discouraged the use of uterine power morcellation in laparoscopic hysterectomy and myomectomy because of serious safety concerns after the accidental use of this technique in women with occult uterine sarcoma (e.g. leiomyosarcoma). Patient outcome with respect to morbidity and mortality may be negatively influenced due to morcellation. [1,2] Unfortunately, the diagnosis of uterine sarcoma is complex since methods to rule out this condition with certainty do not exist. Furthermore, although considered difficult due to a paucity of studies with large series of patients, it was estimated by the FDA that 1 in 350 women undergoing hysterectomy or myomectomy for fibroids will have an unsuspected uterine sarcoma.[3] To prevent the unintentional morcellation of a uterine malignancy, it is proposed to stop using a power morcellator and return to traditional methods such as abdominal laparotomy or vaginal incision to remove the uterus or myoma. Methods to avoid tissue spread such as in-bag morcellation are under investigation. [4-8] In theory contact between tissue and abdominal wall and cavity is avoided, however studies in Urology and Gastroenterology have, in fact, demonstrated port-site metastases after contained morcellation. [9-12] Although these occurrences have been rare and additional risk factors other than morcellation have been proposed, they stress the importance of larger studies to confirm the efficacy of in-bag morcellation in gynaecology. Moreover, before any alternative can be proposed, it is essential to understand the actual problem at hand. Without solid knowledge of the process of morcellation, tissue spread and tumour seeding, it is unlikely that a sustainable solution will be discovered. The aim of our study was to assess the occurrence and amount of tissue spread in the morcellation procedure, and to identify any factors that influence the tissue spread. This study intends to contribute to the development of a more effective morcellation technique. Understanding the pattern of tissue spread may help us find a solution to a serious problem, so that in the future the benefits of minimally invasive surgery will not be lost for women with larger uteri.

Methods & Materials

A prospective observational study was performed from January 2011 till May 2013 at the Leiden University Medical Centre (LUMC) and the St Lucas Andreas Hospital (SLAZ) in Amsterdam. The morcellation procedure in Total Laparoscopic Hysterectomy (TLH) procedures and Laparoscopic Supracervical Hysterectomy (LSH) procedures

were timed and basic procedure and patient characteristics were gathered. Seperately, LSH procedures were recorded for a Time Action Analysis (TAA). All procedures were performed by 4 experts in minimally invasive gynaecologic surgery, except for the procedures in the TAA which were performed by 1 expert. The Gynecare Morcellex (Ethicon, Inc., Somerville, NJ) and LiNA Xcise (LiNA medical, Glostrup, Denmark) were used during the procedures. No distinction was made in the data between the type of used morcellator since the Morcellex and LiNA Xcise rely on the same 'motor peeling' working principle, have by approximation a similar instrument diameter, blade rotation speed, weight, and are disposable.[13] Intra-operative data and basic patient characteristics were gathered. To accurately analyse the morcellation procedure, this procedure was divided into 4 stages: Stage 1 or Tissue manipulation: grasping and manipulation of the uterine tissue toward the cutting blade of the morcellator. Stage 2 or Tissue cutting: morcellation instrument actively cutting tissue, and tissue being pulled through the morcellation tube. Stage 3 or Tissue depositing: morcellation instrument inactive, tissue strip being deposited in a retainer outside the patient, and reinsertion of the grasper through the morcellator. Stage 1 to 3 were used to calculate the total morcellation time. Stage 4 or Cleaning stage: inspection of the abdomen to detect and remove residual uterine tissue pieces, and irrigation of the abdominal area. Tissue spread is determined by counting the number of visually detectable tissue pieces removed during stage 4 through grasping, suction and rinsing. In addition, the duration of stage 4 was used as to further estimate the amount of tissue spread. Morcellation rate is calculated in grams per minute as the weight of the excised tissue divided by the morcellation time. Statistical analysis using the 2-tailed *t* test under assumption of homogeneity of variance was performed for the LSH and TLH groups separately with respect to the TAA group. For the TAA group, procedures were divided into 3 groups according to uterine weight (A: <350g, B: 350-750g, C: >750g). A 2-tailed *t* test was used for identifying significant differences between groups. Standard linear regression analysis was performed to assess the interdependence between recorded variables. A p-value of .05 was considered statistically significant. All patients consented to participate in this study.

Results

A combined total of 52 TLH and LSH procedures were analysed, of which 23 LSH procedures were analysed by TAA. Table 1 shows that no statistical differences were observed in patient characteristics and morcellation related parameters between the procedures that were timed and the procedures that were analysed through TAA. The average operation time was 152 min and 158 min respectively and the morcellation procedure comprises 13% and 15% respectively of total operation time.

Table 1: Patient characteristics and morcellation procedure parameters; comparison between Time Action Analysis Group and remaining group. Data provided as mean (Standard deviation; range)

	TAA group (n=23)		TLH & LSH without TAA (n=29)		p
Age	47	(6,5; 36-68)	45,8	(5,9; 31-57)	.5
Parity	1,1	(1,1; 0-3)	1,6	(1,4; 0-4)	.2
BMI*	24,5	(3,0; 21-32)	27,3	(5,7; 18-40)	.1
Indication for surgery					
- Uterine myoma	18 (78,3 %)		24 (82,8 %)		
- menorrhagia	4 (17,4 %)		4 (13,8 %)		
- dysmenorrhea	-		1 (3,4 %)		
- unavailable	1 (4,3 %)		-		
Total operation time [min]	158	(47; 78-245)	152	(45; 90-332)	.7
Uterine weight [g]	425	(341; 29,5-1260)	377	(237; 75-1265)	.5
Morcellation stage time [min]	24	(19; 3,4-245)	20	(15; 3-74)	.4
Morcellated weight [g]	421	(337; 29,5-1260)	302	(237; 75-1265)	.1
Morcellation rate [g/min]	17,8	(8,0; 8,1-33,9)	17,8	(9,7; 4,5-46,7)	1
Number of excised tissue strips	48,5	(40,7; 2-131)	37.7	(29,8; 9-146)	.3
Average weight per strip	9,7	(4,0; 5,1-19,8)	8.8	(3,5; 4,2-19,3)	.4
Bloodloss [ml]	200	(186; 0-800)	270	(328; 0-1600)	.4

* Data missing from 6 patients in TAA group and 3 in remaining group.

The results from the TAA are provided in table 2. Morcellation conditions were similar in all 3 groups because no significant differences were found in morcellation rate and weight per removed tissue strip. Figure 1 is a graphic representation of the time division of the separate morcellation stages. It shows the stage percentages (stages 1-3) and total morcellation time as compared with the cleaning stage time (stage 4). A large proportion of time is spent on manipulating tissue and depositing tissue, and only a limited amount on cutting the tissue. With increasing uterine weight, the total morcellation time also increased. Analysis of the different stages of total morcellation time showed similar increase for stages 1, 2 and 3, but not for stage 4 (i.e. the cleaning stage). No significant difference was found in the cleaning stage between weight group B (350g-750g) and group C (>750g). No significant difference was found in the number of scattered tissue pieces between groups B and C.

To further analyse the cutting process, the tissue cutting time throughout the morcellation procedure was analysed. The length of every single removed tissue strip was approximated by the time spent cutting that tissue strip in the TAA, thereby

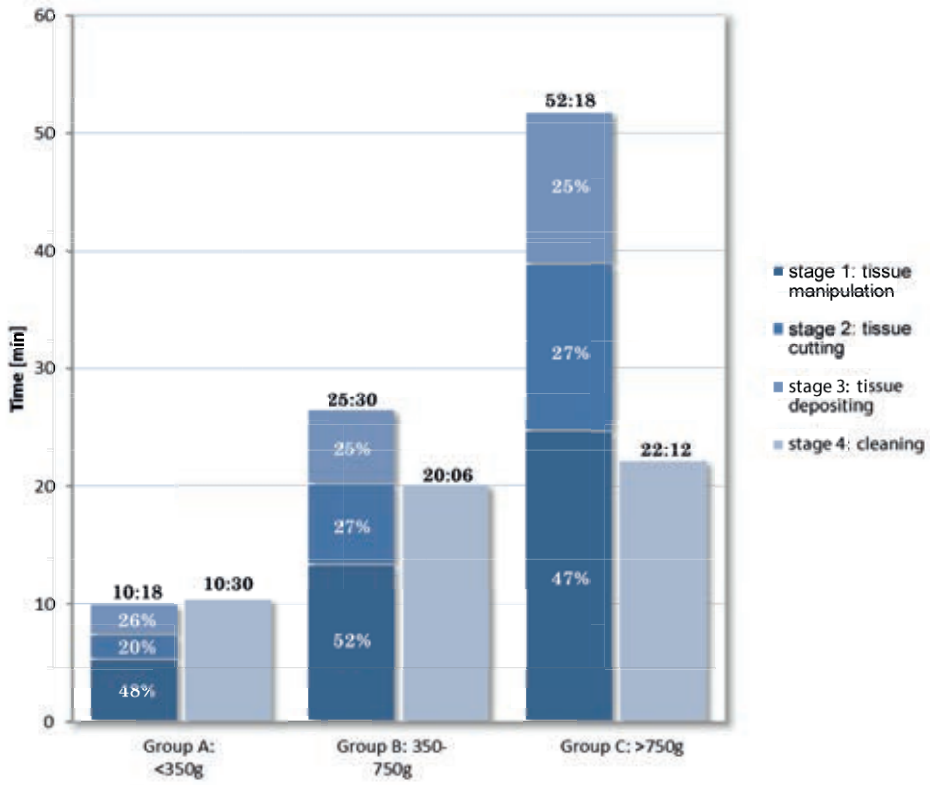

Figure 1: Chart providing the division of morcellation stages in percentages and the morcellation stage and cleaning stage time of groups A, B and C. Note that the presented percentages do not exactly add up to 100% because the percentages are calculated for every separate procedure and the mean is calculated afterwards over the population size.

allowing an evaluation of the change in length of the removed tissue strip during the morcellation process. This resulted in Figure 2, which shows the mean tissue cutting time per tissue strip for all patients combined, as a function of morcellation completion (in percentage). The morcellation completion percentage was calculated as 100 times the n-th tissue strip cutting action divided by the total number of cutting actions required to remove the full mass. The mean tissue cutting time over all patients was calculated for every 2% of morcellation completion. Linear regression analysis through the mean data shows a negative Pearson's correlation coefficient of r = -.,81 (p<.001). This means that the length of tissue strips appears to decrease with progression of the morcellation completion.

Table 2: Patient characteristics and procedure data of Laparoscopic Supracervical Hysterectomy (LSH) group evaluated with Time Action Analysis (TAA), subdivided into categories based on uterine weight. Data presented as mean (Standard deviation; range). Significance calculated with two-tailed t-test under assumption of homogeneity of variance.

Variable	Total (n=23)		Uterine weight:						P Values		
			Group A: <350g (n=11)		Group B: 350g-750g (n=7)		Group C: >750g (n=5)		P_{A-B}	P_{B-C}	P_{A-C}
Total operation time [min]	158	(47; 78-245)	127	(35; 78-182)	178	(44;121-245)	198	(31;165-244)	<.05	-	<.05
Morcellation stage time [min]	24,1	(18,9; 3,4-68,4)	10,3	(4,4; 3,4-16,8)	25,5	(10,6;16,4-47,7)	52,3	(15,2;32,0-68,4)	<.001	<.05	<.001
- **Stage 1: tissue manipulation [min]**	12,0	(9,3; 1,4-36,9)	5,4	(2,8; 1,4-11,4)	13,4	(6,0;6,8-24,8)	24,7	(8,9;13,8-36,9)	<.05	<.05	<.001
- **Stage 2: tissue cutting [min]**	6,1	(5,6; 0,7-19,8)	2,0	(0,7; 0,7-3,0)	6,8	(2,8;2,3-10,9)	14,2	(5,3;6,1-19,8)	<.001	<.05	<.001
- **Stage 3: tissue depositing [min]**	6,0	(4,6; 0,8-15,8)	2,7	(1,5; 0,8-6,2)	6,4	(2,9;4,6-12,0)	12,9	(3,0;9,6-15,8)	<.05	<.05	<.001
- **Stage 4: cleaning [min]**	16,0	(7,3; 3,5-28,8)	10,5	(4,0; 3,5-17,9)	20,1	(6,3;7,5-25,2)	22,2	(5,7;13,5-28,8)	<.001	-	<.001
Weight of excised tissue [g]	421	(337; 29,5-1260)	144	(65; 29,5-238)	499	(138;350-680)	922	(224;680-1260)	<.001	<.05	<.001
Morcellation Rate [1] [g/min]	17,8	(8,0; 8,1-33,9)	15,3	(8,8; 8,1-33,9)	21,5	(8,0;10,4-30,9)	18,3	(4,3;14,6-24,3)	-	-	-
Number of excised tissue strips [-]	48,5	(40,7; 2-131)	16,7	(9,0; 2-38)	55,9	(24,9;23-98)	108,2	(25,2;72-131)	<.001	<.05	<.001
Average weight per strip [g]	9,7	(4,0; 5,1-19,8)	9,8	(4,6; 5,3-19,8)	10,1	(3,9;5,1-16,8)	8,9	(3,0;6,8-13,9)	-	-	-
Tissue scatter pieces [-]	12,8	(9,2; 1-37)	6,7	(5,1; 1-15)	15,1	(7,5;7-29)	22,8	(8,9;14-37)	<.05	-	<.001
Intraoperative blood loss [mL]	200	(186; 0-800)	128	(88; 0-300)	314	(269;50-800)	182	(141;10-400)	-	-	-

[1] Morcellation Rate calculated as Morcellated tissue weight divided by morcellation stage time.

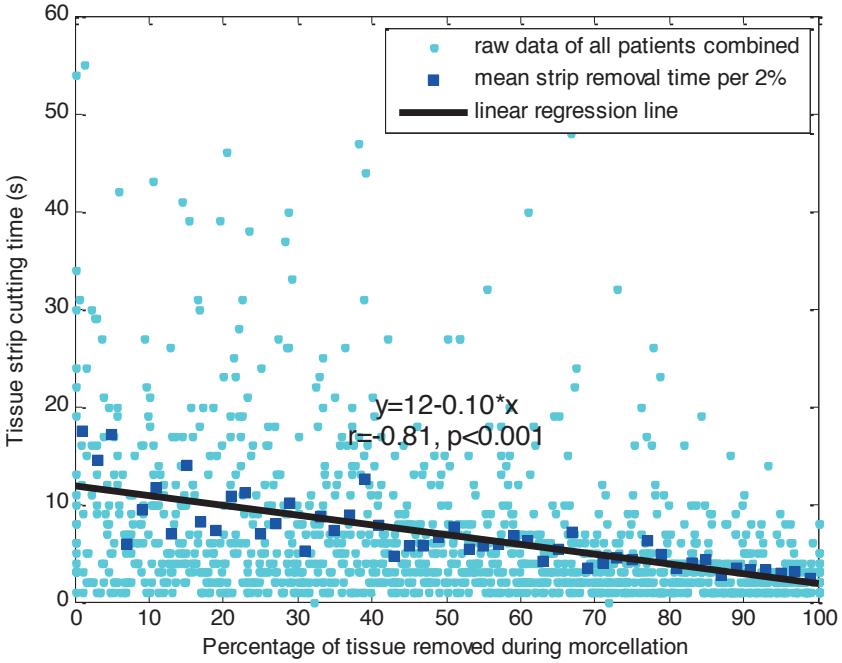

Figure 2: Linear regression analysis for tissue strip cutting time as function of the percentage of removed tissue during morcellation. The percentage of tissue removed is approximated as 100 times the nth tissue cutting action divided by the total number of cutting actions required to remove the tissue mass. Raw data from all patients is used to obtain a mean strip removal time for every 2%. Linear regression analysis is performed on the mean data.

Discussion & Conclusion

This study was performed to provide insight into the 'physiology' of the morcellation process. The complete morcellation process has 4 stages. Overall morcellation time amounts to 15% of the total procedure time on average, showing that morcellation does not account for a large extension of the total operation time. Manipulation of tissue (stage 1) comprises 50% of the morcellation procedure, whereas only 25% of the time is spent on the actual cutting of tissue (stage 2). As expected, the duration of tissue handling, tissue cutting and tissue depositing (stages 1 to 3) increases with larger uteri. In contrast, duration of the cleaning stage (stage 4) did not demonstrate the same linearity. Compared to uteri <350g, more time was spent on cleaning in cases with uteri weighing between 350g-750g. Interestingly, no further increase of stage 4 was noticed when uteri over 750g were compared to uteri weighing 350-750g. The same can be said for the number of scattered tissue pieces during stage 4. Apparently, there seems to be a cut-off point. If the amount of tissue scatter is estimated by the

duration of the cleaning stage (meaning that a longer cleaning stage indicates more tissue scatter), then it implies that tissue scatter increases significantly after this cut-off point, and furthermore that after this point tissue scatter remains constant regardless of uterine weight. It can be cautiously concluded that the amount of tissue scatter is not related to uterine weight, but correlates with a certain cut-off point. To limit the amount of tissue spread with the current technology, power morcellation may only be used until a certain uterine weight. In this study, the cut-off point was found at 350g.

Linear regression analysis of the mean tissue cutting time per tissue strip showed that cutting time decreases as the morcellation process progresses. Using the tissue cutting time to estimate the length of the tissue strips, it can be concluded that at the start of the morcellation process the tissue strips are larger and tissue strips become shorter with progression of the morcellation process. Furthermore, although the range of the raw data is large, 82%, of the tissue cutting action has a duration of less than 10 seconds, and 60% under 5 seconds, both occurring more frequently later on in the procedure. This implies a certain inefficiency in the morcellation procedure, because apparently large pieces of tissue strips are only created at the very beginning of the cutting process. In this light, the rotational mechanism of the current power morcellators should be reconsidered, given that smaller tissue strips are inherently more prone to scatter by the rotating blade of the power morcellator. This rotational mechanism may be an important focus for enhancing the efficacy of the morcellation process regarding tissue spread. A solution may be to enhance the creation of large tissue strips or to assess an alternative for the rotational mechanism. One alternative for this mechanism already exists. The PKS PlasmaSORD (Solid Organ Removal Device) is manufactured by Olympus and it uses bipolar cutting instead of a rotating blade. Unfortunately, it causes smoke and it has been hypothesised that other mechanisms such as the CO_2 pneumoperitoneum, raised abdominal pressure and smoke may contribute to tissue spread.[9] Another important finding of our study is the moment of the morcellation process which is at greatest risk of tissue spread. As stated, over 60% of morcellation time is under 5 seconds, meaning that these tissue strips are small, therefore possibly at risk for spreading. In addition, our study demonstrated these small tissue strips occur increasingly towards the end of the morcellation process, meaning that the risk of tissue spread is highest at the end of the morcellation process. From this it may be concluded that LSH and laparoscopic myomectomy procedures, that do not have a vaginal access, are more prone to tissue scatter since all tissue needs morcellation, compared to TLH procedures in which only part of the uterus is morcellated to the point where the uterine remnant fits through the vagina. A solution to this problem in LSH en LM procedures could be to only use morcellation to the point where the uterine corpus or myoma can be removed vaginally after performing a colpotomy.

Although several studies have been published regarding power morcellators, relatively few comparative or clinical studies exist and some morcellators have been introduced in clinical practice without any (published) studies altogether. [13,14] The main focus of these studies appear to have been technical characteristics such as morcellation rate. It is questionable if upon introduction of power morcellators tissue spread was considered to be a severe side effect of the morcellation process. Gradually reports were published on the iatrogenic spread of benign uterine tissue. It is only afterwards, that information regarding the unintentional morcellation of malignant tissue became available. Naturally power morcellators were never intended for use in case of a malignancy and moreover, any fragmentation of malignant tissue is usually contraindicated in the principles of oncologic surgery.

The weakness of our study is that tissue spread was not evaluated on a cellular level. Instead, the number of macroscopically detectable scattered tissue pieces and the and duration of the cleaning stage were used to determine the amount of tissue spread. Although the complete abdominal cavity and peritoneum were carefully and meticulously searched for tissue spread, it is possible that small tissue fragments were overlooked. Furthermore, the tissue strip cutting time was considered to be representative for the length of the tissue strips. Therefore, any conclusion regarding tissue scatter and tissue strip length should be interpreted with relativism. It was attempted to define the cut-off point of the uterine weight more precisely. A cut-off point calculated on raw data (instead of by comparing the 3 groups according to uterine weight) could not be found due to relatively limited sample size of 23 patients. For the same reason, a confidence interval in which the cut-off point lies could not be calculated. Lastly, the outcome of our study may not be applicable to power morcellators with other technical specifications such as a difference in diameter.

To solve these shortcomings, a TAA of the morcellation process in a larger population is needed to verify the results of this study. Microscopic evaluation of tissue spread and the pattern of tissue spread may be an interesting addition to future studies. Notwithstanding these limitations, this study offers valuable knowledge regarding the basic 'physiology' of the morcellation procedure and tissue spread. Based on the results, the current rotational mechanism of the power morcellators should be reconsidered due to their relative inefficiency with respect to tissue scatter. Furthermore, the partial morcellation of uterine tissue seems less at risk to cause tissue spread compared to complete morcellation. For LSH and LH procedures this means that only part of the uterine tissue should be morcellated after which the remnant tissue can be removed vaginally through colpotomy. In TLH this is already standard procedure.

Finally, solutions that allow morcellation without spread are being investigated and focus mainly on in-bag morcellation. Although in-bag morcellation may be a proper solution for now, it treats a "symptom" rather than the underlying condition. To come to a sustainable solution to the current problem of tissue spread, it is most important that the underlying mechanism is addressed. This study suggests the rotational mechanism as an important factor. It is time for the engineer to further evaluate and enhance the technology of power morcellators.

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Power morcellator features affecting tissue spill in gynecological laparoscopy: an in vitro study

L. van den Haak, E. A. Arkenbout, E. M. Sandberg, F.W. Jansen

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J Minim Invasive Gynecol. 2016 Jan;23(1):107-12

Abstract

Study Objective: To assess features of power morcellators (blade diameter, circular versus oscillating cutting, blade rotation speed, experience level) regarding their effect on the amount of tissue spill. In addition, the amount of tissue spill after the initial two-thirds and final one-third of the morcellated specimen was evaluated.

Design: An in-vitro study (Canadian Task Force classification II-2).

Setting: Laparoscopic skills lab of an academic hospital

Patients: Not applicable

Intervention: Power morcellation of beef tongue specimens

Measurements and main results: Twenty-four trials were performed. Morcellation was performed in 2 phases (phase 1: initial two-thirds of the total tissue, phase 2: last one-third of the tissue). With larger blade diameter a decline was observed in both the weight of the spilled particles (phase 1) and the number of spilled particles (phases 1, 2 and both combined) (weight phase 1= 6.5g vs 6.3gr vs 2.2gr for 12.5mm vs 15mm vs 20mm respectively, p=.04; number particles: Phase 1= 10.2 vs 7.2 vs 2.7 p = .01, Phase 2= 22.9 vs 19.0 vs 8.9 p= .02, Total= 34.7 vs 26.2 vs 11.6 p=.01). Also, spinning of the tissue mass due to torque being applied by the rotating blade occurred later when blade size increased, and the size of the spilled particles was larger (weight of morcellated tissue at onset of torque: 136g vs 198g vs 222g p=.07 and Size: .6g vs .9g vs .8g p=.1). In the oscillation mode, there was less total spill (6.8g/100g versus 21.3g/100g, p=.01, for oscillation and circular cutting respectively)

Conclusion: The present study demonstrates that less spill is created by power morcellators with an oscillating blade and / or a large diameter (≥20mm). Furthermore, when using a large diameter blade the spilled particles are larger and less morcellation repetitions are needed. By combining these features with currently introduced contained morcellation, the safety of the morcellation process with respect to tissue spill can be further improved.

Introduction

The safety of power morcellators for the laparoscopic removal of large uteri and myoma is seriously questioned after reports of the accidental morcellation of occult uterine malignancies. The occurrence of tissue spread, caused by morcellation, is strongly believed to result in an upstage of the disease.[1] As a result, the U.S. Food and Drug Administration (FDA) decided in 2014 to advise against the further use of these instruments in almost all cases.[2] This poses a challenge for the future of minimally invasive gynecologic surgery, since the FDA statement effectively implies a return to laparotomy for numerous hysterectomy and myomectomy procedures. However, it is questionable if this return to laparotomy is sustainable. In fact, it has been argued that a return to this approach in all cases of hysterectomy and myomectomy will lead to higher morbidity, mortality and costs when compared to laparoscopy, even when including the accidental morcellation of uterine malignancies.[3,4] Based on these studies, the morcellation technique should not be swiftly abandoned. However, it is clear that the safety of power morcellation should be enhanced. Currently, research on this topic focusses mainly on contained morcellation techniques, because in theory this should prevent complications due to tissue spread and may also help to prevent direct organ damage by the morcellation blade. Although the feasibility of in-bag morcellation has been demonstrated in several studies [5-7], long term outcomes do not exist and containment bags are even used off-label. Moreover, contained morcellation does not address the shortcomings of current power morcellators. A recent study, demonstrated that tissue spill increases significantly after a certain weight was morcellated and, in addition, that the efficiency of the current instruments may be improved.[8] The goal of this study is to further explore the technical features of power morcellators and their effect on tissue spill during the morcellation process. By clarifying the details of this process we hope to contribute to the development of more efficient and safe instruments and of surgical techniques with respect to tissue spill.

Methods

The following features and their effect on tissue spill were examined in an in vitro setting (table 1):

First, the effect of different blade diameters was assessed. Diameters of 12.5mm, 15mm and 20mm were used. Speed was set at 400 rotations per minute (rpm) combined with standard circular cutting of the blade; Second, oscillation instead of circular cutting was assessed. In the oscillation mode, the morcellation blade rotates alternately 4 times clockwise and 4 times counter-clockwise; Third, the effect of rotation speed of the morcellation blade was evaluated. For this purpose, the speed was set at 800 rpm and

compared to 400 rpm; Fourth, the effect of experience level was studied, by comparing the results of the expert with a novice (LH, a resident in obstetrics and gynecology), Finally, the point in time (defined as the weight of tissue already morcellated) was evaluated where the tissue cutting action unintentionally shifts to torque being applied to the tissue mass due to friction, and as a result, the tissue mass starts rotating uncontrollably with the blade.

Table 1: experiment design

	12.5 mm	15 mm	20 mm
Diameter [a]	4 trials	4 trials	4 trials
Oscillation [b]		4 trials	
Speed [c]		4 trials	
Novice [d]		4 trials	
Total	24 trials		

[a] Standard setting: speed 400 rpm, circular cutting
[b] Oscillation mode: 4 rotations clockwise alternated by 4 counter-clockwise. Speed 400 rpm.
[c] 800 rpm was compared to 400 rpm.
[d] Novice: 2nd level according to the ESGE Standard Laparoscopy

All trials were performed by an expert in minimally invasive gynecologic surgery (FWJ), except for the novice trials. In agreement with other in vitro studies, beef tongue was used to simulate uterine tissue. [5,9,10] Pieces of 400-500 grams were morcellated. To collect all tissue spill, the morcellation specimen was placed in a clear plastic bag in an open laparoscopic box trainer (fig 1).

Figure 1: The test setting in an open laparoscopic box trainer.

The Blue Endo MOREsolution Tissue Morcellation System (Benetec Advanced Medical Systems, Retie, Belgium) power morcellator was used to perform all tests.[11] The system allows the use of 3 different diameters with the same instrument and power settings, thereby ensuring that measured differences can be attributed to diameter alone and not to instrument-specific features. Moreover, the MOREsolution provides circular cutting as well as oscillation, and adjustable blade rotating speed.

All trials consisted of 2 phases. First, the intitial two-thirds of the beef tongue specimen was morcellated. The weight of the morcellated tissue was subtracted of the total specimen weight to determine the cut-off point. Next, the remaining one-third of the tissue (minus the spilled particles) was transferred to a new, clean bag and morcellation continued until all tissue was morcellated. The 2 bags were then inspected for macroscopic tissue spill. Spill was defined as any remaining tissue that could be extracted via the morcellator tube without activation of the morcellator. All tissue spill particles were counted and weighed.

The primary outcomes are number and weight of spilled particles (phase 1, phase 2 and both combined), duration of the morcellation procedure, the morcellated tissue weight at the onset of torque, the number of morcellation repetitions (meaning the number of tissue strips removed by the morcellator) and the size per spilled particle (weight per particle). All results (except for time and torque) are standardised for comparison, by calculating the outcome per 100 gram of morcellated tissue. Non-parametric tests (the Mann-Whitney U and Wilcoxon signed-rank test) were used to analyse all data. The Jonckheere-Terpstra test was used to evaluate the presence of trends in the studied diameters. All results are shown as median values, unless otherwise specified. $P \leq .05$ was considered significant.

Results

Twenty-three trials and 1 test trial devided over 6 groeps were performed (table 1). For all groups combined, the mean weight of beef tongue was 431 grams (380-504g). During phase 1 and 2, 63% and 30% of the total weight was morcellated respectively. Mean weight and percentage of weight morcellated during phase 1 and 2, did not differ between groups. (table2)

Table 2: Results

	Total weight[a]	Phase 1 (% of procedure)	Phase 2 (% of procedure)	Particles[b] phase 1 (n)	Particles[b] phase 2 (n)	Particles[b] total (n)	Weight[b] phase 1	Weight[b] phase 2	Total weight[b]	Morcellation repetitions(n)	Weight per spill particle[b]	Weight at onset of Torque[d]	Time
12.5mm	400 (385-434)	60 (57-63)	33 (24-35)	10.3 (4.3-15.1)	22.9 (18.9-38.1)	34.7 (23.0-50.0)	6,2 (1,6-11,9)	11,2 (9,2-27,6)	15.9 (13.7-39.5)	13,7 (9,5-18,5)	.6 (.3-.8)	136 (80-184)	18 (14-18)
15mm	458 (391-496)	61 (53-69)	30 (23-39)	7.2 (2.3-8.9)	19.1 (16.8-32.5)	26.2 (21.4-41.3)	6,3 (1,5-9,3)	16,9 (11,3-31,5)	21.3 (17.1-38.2)	10.2 (9.2-11.3)	.9 (.5-1.1)	198 (147-260)	11 (7-18)
20mm	453 (428-504)	65 (62-71)	29 (26-36)	2.7 (1.0-5.9)	8.9 (4.4-19.5)	11.6 (5.4-25.4)	2.2 (,3-3,3)	10,5 (3,9-14,1)	12.7 (4.2-17.4)	4.3 (4,2-4,4)	.8 (.7-1.3)	222 (100-240)	6 (1-6)
Oscillation	386 (380-418)	68 (64-69)	26 (23-29)	6.6 (4.3-8.7)	16.4 (13.9-21.1)	22.7 (18.9-29.8)	[c]	[c]	6.8 (6.5-7.8)	6.3 (6.0-7.5)	.3 (.3-.4)	232 (161-268)	10 (8-13)
800 rpm	473 (391-496)	62 (53-64)	30 (24-39)	7.4 (2.3-8.8)	22.8 (16.8-32.5)	29.0 (21.4-41.3)	6.3 (1.5-6.7)	16.6 (11.3-31.5)	20.5 (17.6-38.2)	10.2 (9.2-11.3)	.8 (.5-1.1)	198 (147-260)	11 (9-12)
Novice	419 (402-437)	59 (58-63)	34 (33-35)	6.9 (2.8-7.3)	18.2 (16.8-23.5)	25.3 (19.6-30.4)	4.7 (.8-5.5)	11.9 (9.9-13.1)	15.8 (13.0-17.8)	7.0 (5.8-9.7)	.6 (.5-.7)	142 (101-154)	18 (13-26)

Numbers are median (range). [a] All weight in grams, [b] particles and weight per 100grams of morcellated tissue, [c] missing data, [d] onset of torque displayed as the amount of tissue morcellated so far (in grams)

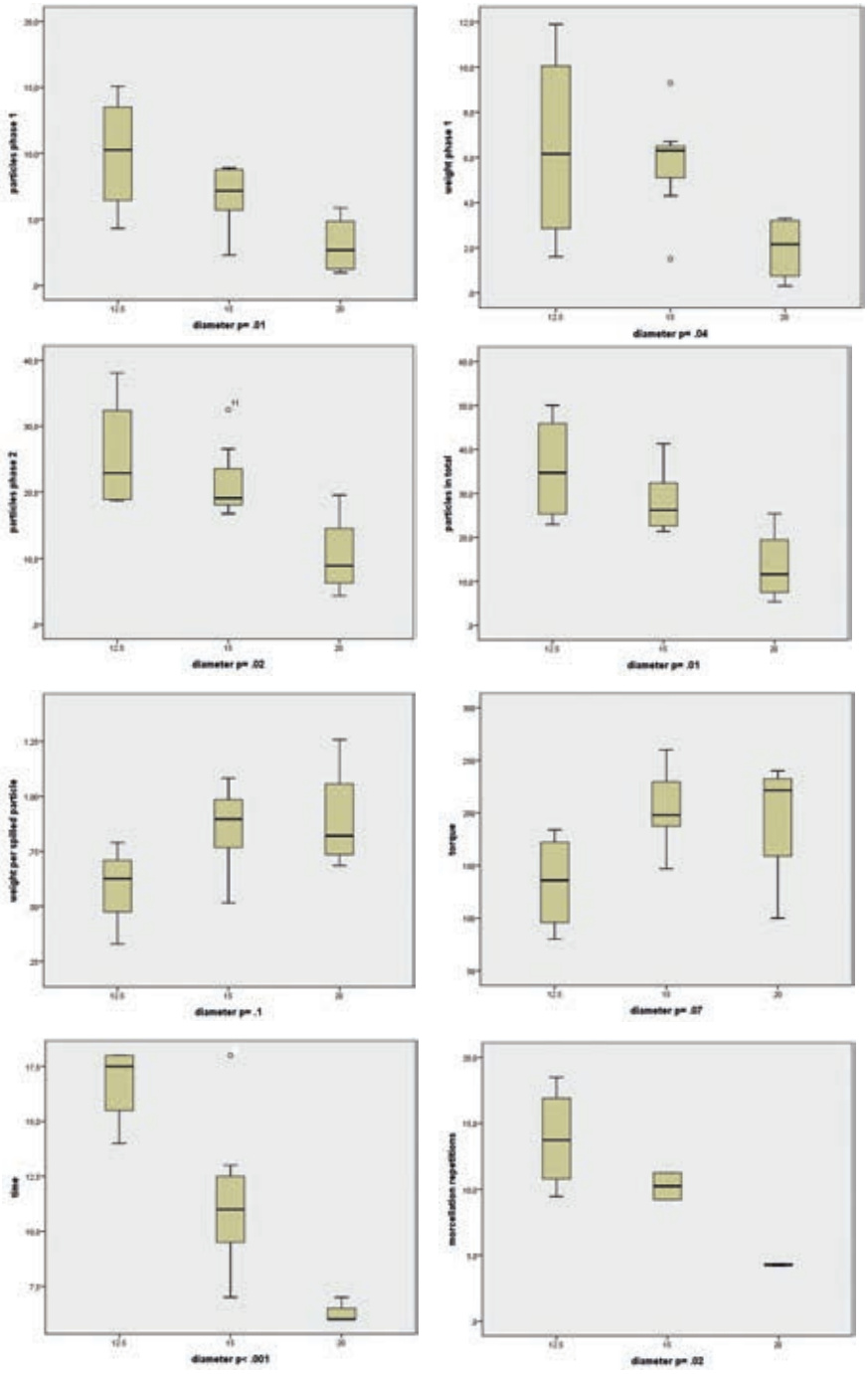

Fig 2 outcome of Jonckheere-Terpstra test. Diameter (mm), weight (g/100g), particles (n/100g), time (min), torque (grams morcellated weight)

With a larger diameter, both the weight of the spilled particles (phase 1) and the number of spilled particles (phase 1, 2 and in total) declined (weight phase 1= 6.5g vs 6.3g vs 2.2g for 12.5mm vs 15mm vs 20mm respectively, p=.04; number particles: Phase 1= 10.2 vs 7.2 vs 2.7 p = .01, Phase 2= 22.9 vs 19.0 vs 8.9 p= .02, Total= 34.7 vs 26.2 vs 11.6 p=.01). Also with a larger diameter, morcellation was quicker and less morcellation repetitions were needed (time for total procedure: 18min vs 11min vs 6min p<.001 and repetitions: 13.7 vs 10.2 vs 4.3 p=.02). Finally, the onset of torque applied to the tissue mass occured later and the spilled particles were larger (Torque: 136g vs 198g vs 222g p=.07 and Size: .6g vs .9g vs .8g p=.1). (fig 2), although these differences were not statistically significant.

In the oscillation mode, there was less total spill per 100g (6.8g/100g versus 21.3g/100g, U=.000, p=.01, for oscillation and circular cutting respectively) and spilled particles were smaller (.3g/particle vs .9g/particle, U=.000, p=.01).

The novice created smaller spilled particles (.6g/particle vs .9 g/particle, U=.000, p=.02, for novice and expert respectively) and the onset of torque applied on the tissue mass occurred sooner (after 142g vs 198g, U=.000, p=.02). Also, morcellation by the novice was significantly slower (18min vs 11min p=.02).

No significant differences or trends were observed between rotation speed of 800 rpm and 400 rpm.

Finally, comparing phase 1 and 2 of all diameters of the expert trials with circular cutting, more spillage (particles and weight) occurred in phase 2 (6.0 particles/100g vs 19.0 particles/100g, T=120 p= .001 and 4.3g/100g vs 13.9g/100g, T=120 p=.001 for phase 1 and 2 respectively; data not shown).

Discussion

Technical features of power morcellators and the morcellation process are assessed in this study. When a larger diameter morcellation blade was used, tissue spill was significantly reduced, less morcellation repetitions were needed, and the procedure was faster when compared to smaller diameters. Next, our study confirmed our previous finding that more tissue is spilled later in the morcellation process. [8] Additionally, it is strongly suggested that the onset of torque applied to the tissue mass occurs later. This implies that this onset of torque may be prevented when a large diameter blade is used combined with partial instead of complete morcellation. Finally, the spilled tissue particles are larger. This may be advantageous since larger spilled particles are easier to detect and remove and are less likely to escape from containment bags.

Interestingly in the oscillation mode, although no effect was found on the onset of torque to the tissue, less total spill was observed when compared to circular cutting. It appears that less spill is an inherent quality of the oscillation mode. It is questionable if the oscillation mode is optimal in the used morcellator: a cycle of 4 turns clockwise is alternated by the same cycle counterclockwise, still allowing the blade to apply torque on the tissue. In theory, it is expected that reducing the cycle to a 1x1 movement may further delay or even prevent torque being applied to the tissue, however this has to be confirmed in future studies.

The differences in the onset of torque and size of spilled particles as observed in the novices trials underline the technical skills that are needed to morcellate tissue. More "coring" and less "peeling" of tissue occurred in the trials of the novice. Although this study was not powered to evaluate a learning curve, a sharp reduction in the morcellation time was found in the 4 trials of the novice (26min to 13 min). When teaching morcellation to a novice, the "peeling" motion should be emphasized and spillage should be carefully monitored.

In all, the results from our study appear to be in contrast with new developments in minimally invasive surgery with respect to minimizing the size and number of key holes during laparoscopic procedures in vivo. Our results suggest that power morcellators with oscillating blades and a large diameter, of 20mm or perhaps more, are advantageous with respect to the amount of tissue spill. Furthermore, less spill is produced when tissue is only partially morcellated. In case of total laparoscopic hysterectomy (TLH) , larger instruments can be readily used by morcellating vaginally. In addition, removal of the larger remnant after partial morcellation should not be difficult via the vagina. However, in case of laparoscopic myomectomy (LMM) or laparoscopic supracervical hysterectomy (LSH), an enlargement of the port-site may be necessary to accommodate larger instruments and to extract the remaining tissue. This can be achieved abdominally, or vaginally by culdotomy.

The current developments in contained morcellation may appear to obviate the need for more efficient power morcellators. However, evidence questions the protective value of contained morcellation in high stage/grade tumors.[12,13] Therefore additional measures should be considered given the often high grade, aggressive characteristics of uterine sarcoma. Furthermore, it has been established that the integrity of morcellation bags can be impaired after use, even when the bags appear intact on gross examination. [14,15] Larger particles are less likely to pass through small puncture holes in the bags, and in case of abdominal spillage, are more easily detected. Finally, less morcellation repetitions decreases the risk of puncture by the device.

Because our experiment was not performed by classical laparoscopy, it may be questioned if our results are clinically applicable and this may be considered a weakness of our study. Our study was intended to examine the technical features of the morcellation instrument and process. By using a box trainer, our results are not affected by laparoscopic skills or the limitations of minimally invasive surgery as such. Furthermore, the use of beef tongue specimens instead of (human) uterine tissue and/or fibroids may be questionable in this context. Although beef tongue has been favorably used in other in vitro studies [5,9,10], its structure may not be completely similar to human fibroid tissue. Fibroids often are inhomogeneous due to calcifications or necrosis, and because of this, the pattern of tissue spread could be different than what we observed. However in our opinion, the inhomogeneity of fibroids may actually cause more tissue spread than the ideal model of beef tongue. Our definition of tissue spill in phase 1 and 2 could be considered artificial. After phase 1, all remaining large tissue particles were transferred to phase 2 and then morcellated. Of course during surgery, morcellation is a continuous process. Moreover, by using the same morcellator for all experiments, the difference in technical features of morcellator was excluded as an influence on the results. As a consequence, however, the outcome from our study may not apply to other commercially available morcellators. Nevertheless, our results are in agreement with previous observations in a clinical setting in which different morcellators were used.[8] Finally, we are aware of the limited sample size of this study. However, large differences were found that were statistically significant even in this sample. Furthermore, it was calculated that, based on our results, only 10-15 trials are necessary to make the trends in torque and particle size significant. Notwithstanding these shortcomings, the results of our study are highly relevant as they finally allow specific recommendations on the morcellator features. Moreover, our recommendations are easy to implement in daily practice and may contribute to safer a morcellation process regarding tissue spill in the very near future. In addition, our study can be used by the health care industry to improve and extend the range of existing power morcellators with oscillating blades and large diameter.

In conclusion, the results from our study demonstrate that tissue spill can be further decreased by using power morcellators with favorable features. Contained morcellation alone has yet to be proven effective, and its shortcomings have been demonstrated. The combined use of in-bag morcellation and more effective power morcellators may well lead to the enhanced safety of this procedure.

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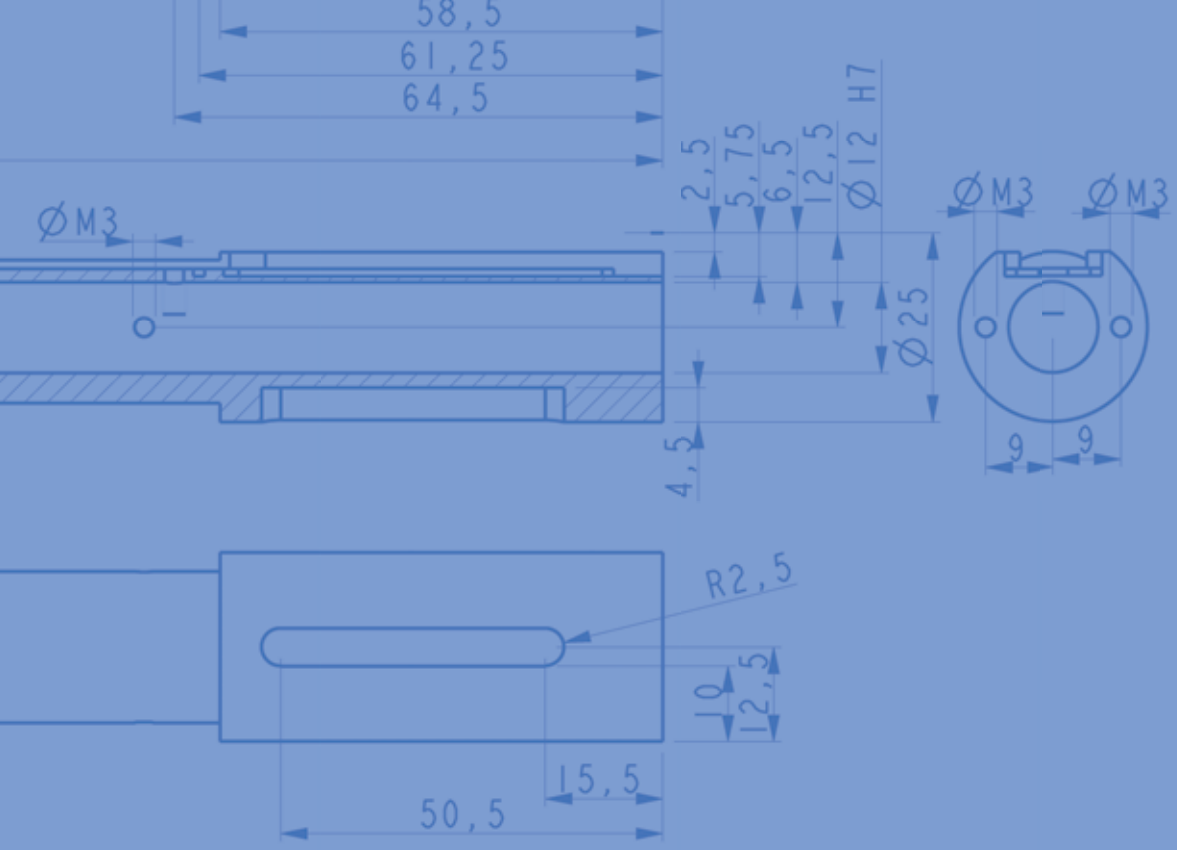
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A laparoscopic morcellator redesign to constrain tissue using integrated gripping teeth

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A. Vierwind, L.E. van Cappelle, F. W. Jansen, J.C.F. de Winter

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J. Med. Devices 11(1), 011005

Abstract

Laparoscopic hysterectomy is a procedure that involves the removal of the uterus through an abdominal keyhole incision. Morcellators have been specifically designed for this task, but their use has been discouraged by the Food and Drug Administration since November 2014 because of risks of cancerous tissue spread. The use of laparoscopic bags to catch and contain tissue debris has been suggested, but this does not solve the root cause of tissue spread. The fundamental problem lies in the tendency of the tissue mass outside the morcellation tube to rotate along with the cutting blade, causing tissue to be spread through the abdomen. This paper presents a bio-inspired concept that constrains the tissue mass in the advent of its rotation in order to improve the overall morcellation efficacy and reduce tissue spread. A design of gripping teeth integrated into the inner diameter of the morcellation tube is proposed. Various tooth geometries were developed and evaluated through an iterative process in order to maximize the gripping forces of these teeth. The maximum gripping force was determined through the measurement of force-displacement curves during the gripping of gelatin and bovine tissue samples. The results indicate that a tooth ring with a diameter of 15 mm can provide a torque resistance of 1.9 Ncm. Finally, a full morcellation instrument concept design is provided.

Keywords: laparoscopic devices, minimally invasive surgery, morcellation, tissue spread, tissue constraining

Introduction

In laparoscopic hysterectomy and myomectomy, tissue needs to be removed without compromising the integrity of the minimally invasive procedure. The power morcellator is an instrument designed for this purpose, having a fast rotating cylindrical blade that allows for the division and removal of tissue.

The Food and Drug Administration (FDA) issued a press release in November 2014, discouraging the use of power morcellators because of their risk of spreading cancerous tissue within the abdomen and pelvis in women with unsuspected uterine sarcoma [1]. It has been estimated by the FDA that 1 in 350 women undergoing hysterectomy or myomectomy for myomas will have unsuspected uterine sarcoma [1,2]. Although this statement has been refuted and is believed to be closer to 1 in 1,550 [3], these FDA statements nonetheless led to the restriction of morcellation, thereby limiting many women with symptomatic leiomyomas to total abdominal hysterectomies. Over the eight months following the FDA safety communication, a decrease of laparoscopic hysterectomies was observed together with an increase in abdominal and vaginal hysterectomies, as well as an increase in major surgical complications and hospital readmissions [3,4]. Concerns have been raised with respect to potentially higher patient morbidity and the long-term outcome of surgical techniques that are adopted as alternatives to standard power morcellation, such as the use of containment bags, vaginal incisions, and intraoperative biopsies [5]. Although complications of morcellation are rare, both the development of parasitic fibroids and the spread of sarcoma cells in the abdominal cavity have been reported [6-8]. Clearly, the issue of tissue spread caused by current power morcellators is one that requires solving.

Cause of Tissue Spread

Tissue spread is the result of a fundamental problem in morcellators that rely on the 'motor peeling' mechanism [9]. The morcellation process constitutes the repetitive grasping, cutting, and disposing of tissue strips sliced from the main tissue mass. Initially relatively long tissue strips are created. With progression of the morcellation process, that is, after the first few tissue strips have been cut and removed, the created tissue strips become shorter [10]. An explanation for this phenomenon is that the tissue mass decreases in size and weight and becomes increasingly distorted in shape. Consequently, the tissue mass itself becomes prone to being dragged along with the fast rotating cutting blade because of friction between the two. Eventually the entire tissue mass may start rotating along with the cutting blade, thereby scattering tissue fragments throughout the intraperitoneal area.

In Figure 1, the tissue spread problem is depicted in detail in three separate instances from left to right: 1) initiation of tissue morcellation, 2) during morcellation, and 3) morcellation failure. When initiating a morcellation action (Fig. 1, left), the tissue mass is grabbed and pulled into the morcellation tube. In the beginning, the length of the tissue strip sliced thus far (through application of force F_{pull}) is short and unable to twist significantly. Accordingly, the surgeon has proper control through force F_{pull}. However, as the slicing of the tissue strip continues, the length of the strip increases and friction between the cutting blade and the main tissue mass outside the tube can induce spinning of the mass (through force F_T), with twisting of the tissue strip as a result (Fig. 1, middle). Spinning of the main tissue mass is especially prominent when the cutting blade has dulled during its use, for example, due to having morcellated calcified myomas or unintentional grasper-blade contact. Literature shows that a high force level is required to achieve steady-state cutting when the blade sharpness is low [11-16]. Thus, when morcellating with a dulled cutting blade, a high force F_{pull} is required to cut the tissue. A low F_{pull} will maintain tissue-blade contact but not initiate cutting, resulting in the tissue mass rotating along with the blade.

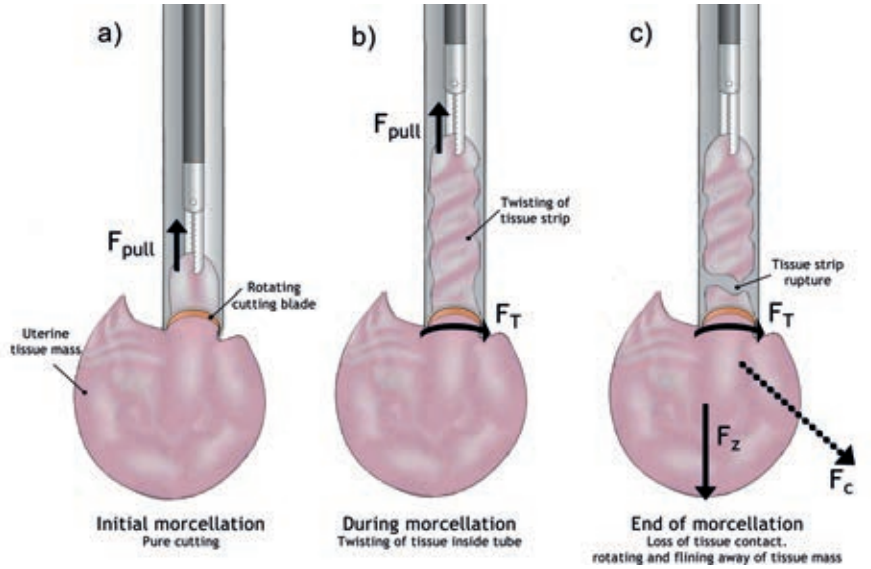

Figure 1: Representation of the tissue mass spinning problem underlying power morcellators. (a) Initiation of morcellation where tissue is pulled into the morcellation tube (F_{pull}) and a tissue strip is being cut properly. (b) Midway through morcellating a tissue strip, where the strip has come to be of such length that twisting of the strip inside the tube occurs. This results in a (possible) torque (F_T) of the tissue mass, induced by the rotating cutting blade, spinning the tissue. (c) Morcellation failure due to rupturing of the (twisted) tissue strip inside the tube. The tissue mass is free to follow the torque F_T as well as disconnect from the morcellation tube (F_z), resulting in a combined force vector F_c, indicating the direction to where the tissue mass falls or is flung. Note: force-vectors not to scale.

The shape of the mass, which is initially roughly spherical, is deformed due to the excision of tissue strips, increasing the likelihood of tissue scatter during tissue mass spinning. Rotation of the mass may lead to rupturing of the tissue strip (Fig. 1, right), after which the tissue mass is free to rotate with the cutting blade (F_T) and disconnect from the distal end of the morcellation tube (e.g., through gravitational force F_z). The combination of forces results in a force vector Fc, in which direction the tissue mass either falls (at low F_T) or is flung away (at high F_T).

State-of-the-Art

In order to provide a brief overview of the state-of-the-art with respect to morcellators, a patent search was performed in the Espacenet database using the search terms *morce* AND (instr* OR tool* OR device*)*, providing 84 results. Filtering these results on title and abstract on relevance with respect to laparoscopic uterine tissue morcellation (excluding intra-uterine shavers), and removing duplicate patents from the same applicants that describe different or updated facets of the same instrument design, yielded a list of 45 relevant patents. Note that this patent search is not all-inclusive as morcellator patents may exist that do not contain the string *morce**.

Standard morcellators that rely on the 'motor peeling' working principle are abundant, where the differences between patents mostly relate to aspects such as reusability versus disposability, instrument dimensions, and cutting blade drive mechanisms [17-25]. Patents of existing morcellators include the LiNA Xcise (LiNA Medical, Glostrup, Denmark) [23], Gynecare Morcellex (Ethicon, Inc., Somerville, NJ, USA) [17, 21], and Storz Rotocut G1 (Karl Storz GmbH & Co, Tuttlingen, Germany) [26]. For a full list of current morcellators used in clinical practice, one may refer to Driessen et al. [9]. Alternative cutting mechanisms include oscillating or vibrating cutting blades [27,28], electrosurgical cutting [29-36], waterjet cutting [37], grinding [38], or the use of a wire mesh to slice tissue [39-41]. Each of these alternative cutting methods have their own strengths and weaknesses. An instrument having an oscillating cutting blade is the MOREsolution Tissue Morcellator (AxtroCare/BlueEndo, Lenexa, KS), which alternately turns four times clockwise and four times counterclockwise. Although this instrument has shown to provide less tissue spread when in oscillation mode as compared to rotation mode [42], the oscillating mode still uses full blade rotations. Electrosurgical cutting speed is dependent on power settings [43], and smoke may obscure the surgeon's vision [44] and contain carcinogenic agents [45]. Using waterjet cutting as a morcellation method macerates the tissue, potentially creating tissue spill in the process, and making histological evaluation no longer possible [46]. Lastly, wire mesh cutting is a method that encapsulates the tissue mass and subdivides it into multiple smaller pieces by drawing the wire mesh through the tissue [39-41]. This method may be time-consuming, as the time required to manipulate a tissue mass into the encapsulating bag has been reported to range from 1 to 13 minutes [47, 48].

To catch and contain tissue spread, a number of laparoscopic tissue entrapment bags have been proposed, each with their own material properties with respect to robustness against perforations and number of openings [49-58]. Following the FDA safety communication, several studies have been performed to evaluate the safety and applicability of such bags in combination with current morcellators [47, 59-61]. Alternatively, several patents describe the bag as inherent parts of the morcellation mechanism [29,32,62-65].

Lastly, the transport of tissue through the morcellation tube can either be done manually, as is current standard practice using a laparoscopic grasper, or automatically, either through suction [29,32,64,66], an internal auger [38], or screw thread [67]. The method of tissue transport strongly relates to the way the surgeon is able to control the uterine tissue mass. The standard morcellator with a laparoscopic grasper may cause tissue scatter problems as described above, whereas automated transport mechanisms usually have some additional way of constraining the tissue. Three patents specifically describe mechanisms that provide improved tissue control [68-70]. The first patent describes an additional instrument that constrains the tissue mass and allows it to be presented to the morcellator in the best way possible [68] (Fig. 2a). The remaining patents describe a morcellator with grasping jaws at their distal end to confine the tissue at the time of cutting (Figs 2b and 2c). The use of such components is beneficial to close the force loop near the cutting mechanism.

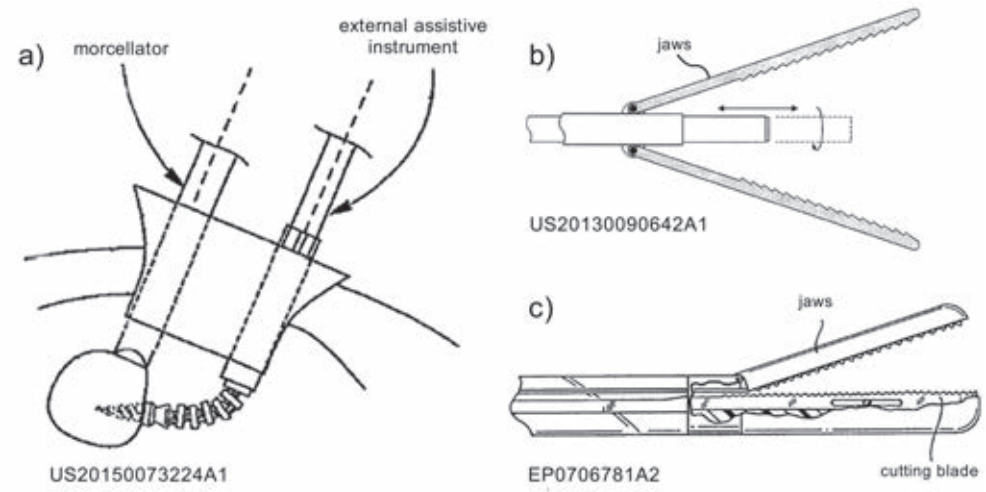

Figure 2: Patent morcellator designs that engage and constrain the main tissue mass during morcellation. (a) patent US20150073224A1. (b) patent US20130090642A1. (c) EP0706781A2. Images cropped and component numbers removed from original patents.

Proposed solution

Solutions identified in the literature to solve the issue of tissue spread are to introduce an alternative cutting method, to encapsulate the specimen being morcellated, or to enhance the efficacy of the rotational cutting mechanism itself. The use of an alternative cutting method has already been explored extensively, but the rotating cutting blade method has remained the standard. The use of a bag is feasible but does not address the source of the problem that causes tissue spread. Furthermore, studies have shown that up to 30% of bags used to contain morcellation spillage may exhibit leakage [71-73], and contained morcellation may not prevent metastasis of high-grade tumors, despite having used a bag [74, 75]. The current research focuses on enhancing the efficacy of the current 'motor peeling' principle to reduce tissue scatter, an approach that may be complementary to the use of bags. Our approach locally confines the tissue mass during morcellation, such as shown in the patents presented in Figures 2b and 2c, thereby preventing the tissue mass from spinning with the rotating blade. Our design differs from those shown in Figure 2 in that the method of tissue confinement is integrated in the standard morcellation instrument, rather than using an external fixation method such as the jaws shown in Figures 2b and 2c. Moreover, our design does not require a change in the standard tissue cutting method.

Concept Design

Many animals can be found that make clever use of tooth geometries and configurations. For example, a method seen in nature for holding and swallowing (slippery or struggling) prey are the large and backward facing pointed papillae that cover the tongue and roof of the mouth of the penguin for eating arrow squids [76], or the upper and lower jaws of the leatherback sea turtle to aid in the consumption of jellyfish [77,78]. Examples of animals that prey on fish or mammals larger than themselves are the cookie cutter shark (Isistius brasiliensis) and the lamprey (Petromyzontiformes, Fig. 3a), which both behave much like a morcellator. Using a mouth and saw teeth that are adapted for sucking, the small shark maintains an attachment to its prey, and is able to slice and scoop out chunks of tissue by using its lower band of saw teeth while rotating its entire body [79, 80]. Similarly, using suction and a vast array of teeth arranged in whorls around the mouth opening, the lamprey attaches itself to other fish. The tongue, also having teeth, is subsequently used to rasp away flesh from the host.

Taking cues from nature, a viable solution to improving the efficacy of morcellators may be through the integration of teeth to provide grip on the tissue mass. In specific, these teeth should compensate for forces FT and FZ. An example of a morcellator design we have created with this principle in mind is provided in Figure 3b, where teeth have been

integrated into the instrument tip. In order to investigate the potential of this solution, a proof-of-principle design has been made of a single ring of teeth. These teeth are required to generate a reaction force close to the location where force FT is generated by the blade, thereby locally closing the force-loop in the event of spinning of the tissue mass. The teeth should engage the tissue mass only when it starts to rotate with the blade, and not hinder the normal tissue debulking process of the morcellator.

The design of the ring of teeth (Fig. 3c) is such that it can be placed coaxially on the inside of the circular rotating blade, at the distal end of a standard morcellation tube. The geometry and orientation of the teeth ensure that they hook into the tissue mass when it starts to rotate with the blade. The teeth are angled inwards, into the morcellation tube, freely allowing the tissue to be pulled up the tube, but blocking it from sliding back into the peritoneal area.

This paper presents research into the dimensions and number of teeth to achieve an optimal gripping force on the tissue mass, whilst still allowing the pulling of the debulked tissue strip through the morcellation tube. Test-bench trials have moreover been performed to assess the grip strength of the teeth on animal muscle tissue.

Figure 3: (a). Lamprey. Image edited to only show the mouth [93]. (b) Lamprey inspired morcellation instrument tip, having integrated teeth for tissue traction. (c) Design of a single teeth ring. Dimensions are in millimetres.

Method

The measurements and validation of the proposed design was performed in two stages together comprising six measurement sessions. Firstly, through porcine gelatin tests (measurement sessions 1–4) teeth of various dimensions were assessed in order to motivate the design choices made in prototyping a single teeth ring. The second stage of tests (measurement sessions 5 & 6) provided the quantification of this ring in terms of gripping strength when using bovine muscle tissue. For all measurements, a

force-displacement curve was obtained by drawing a sample of gelatin or animal tissue past the teeth. The sequence in which the six measurements sessions were performed is shown in Figure 4. The selection process of tooth geometries based on measured forces is described in the subsequent Methods sections (see also Fig. 4, 'selection' boxes); the actual force values are provided in the Results section.

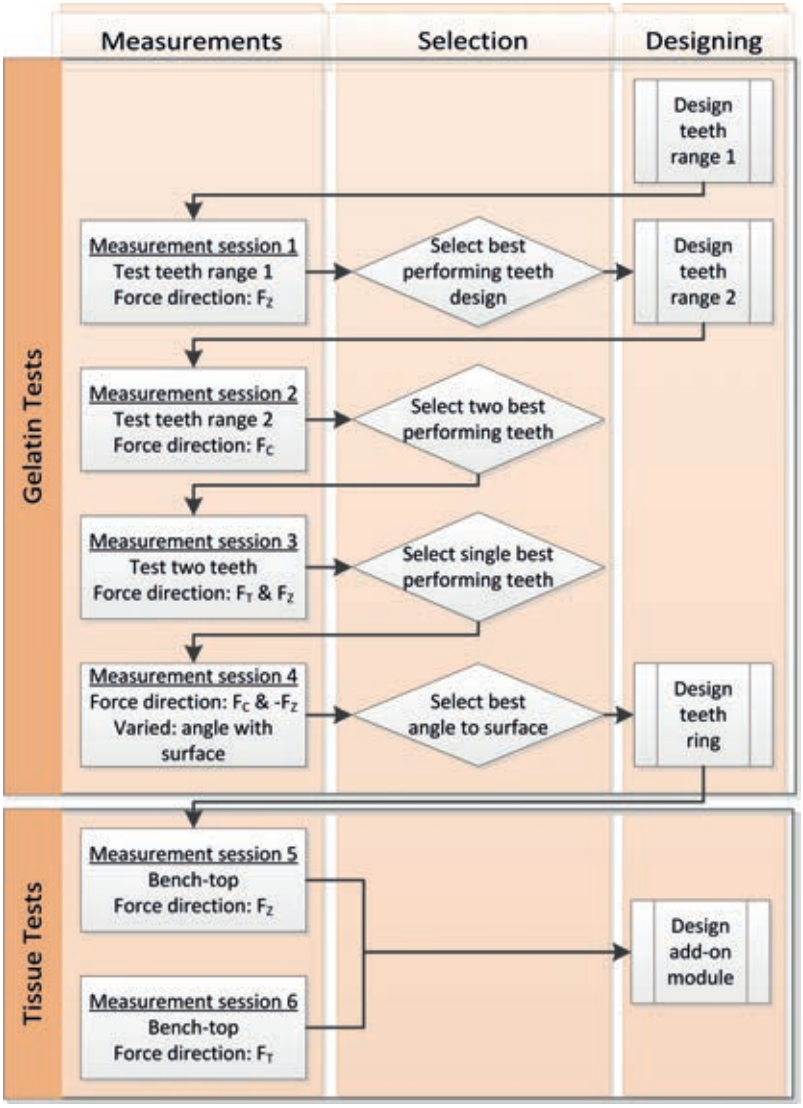

Figure 4: Flowchart of the sequence of measurements performed, where at each measurement a force-displacement curve was generated. In measurement sessions 1–4, porcine gelatin samples were pulled over the indicated teeth in the directions F_T, F_C or F_Z (Fig. 1), using the test setup shown in Figure 5. In measurement sessions 5 and 6, animal tissue samples were pulled in directions F_Z and F_T, in contact with the teeth ring, using the test setup shown in Figure 7.

Teeth optimization for tissue grip – Gelatin tests

To study the tooth geometry and measure their maximum gripping force, a test setup was created as shown in Figure 5. A 1.0 mm thick metal plate, containing sets of teeth, could be placed under an angle of 30°, 45° or 60° with respect to the smooth horizontal surface (see annotation in Fig. 5b), so that only the teeth were protruding upwards. A spring-loaded mechanism under the metal plate was used to center the plate parallel and flush with respect to the surface. Two metal plates of various sets of teeth were created (Fig. 6). The three angles with respect to the horizontal surface were chosen to span a range that is likely to show an influence on the measured forces. Only three angles were assessed to keep the number of measurements to a manageable size. Assessing the fine-grained influence of the gripping angle is left for future research.

Measurements involved placing a set of teeth in the middle of the surface, and a gelatin sample in front of them. The gelatin sample consisted of 15% gelatin and 85% water. A pulling wire (fishing thread, 0.2 mm diameter) ran from a load cell (Futek LSB200, 10lb), having a force measurement range of 0 to 45 N and resolution of 0.038 N, to the gelatin block and back. The wire was placed around the sample with a small plate at the back, allowing the pulling force to be distributed equally over the back surface of the sample. The load cell was attached to a linear stage having a movement step size of 1 μm and speed of 1.25 mm/s. By generating a force-displacement curve while drawing samples past the teeth, the peak gripping force (i.e., the highest measured force, F_{max}) could be measured in different pulling directions (F_Z, F_T and F_C, Fig. 5). For each sample, the front-facing surface contacting the teeth had dimensions 24 x 17mm. A roof plate was placed closely above, but initially not contacting, the gelatin samples (not shown in Fig. 5), vertically constraining them from (upwards) escaping the grasp of the teeth. The friction forces resulting from contact between the sample and both the horizontal surface and the roof plate were measured separately and subtracted from the

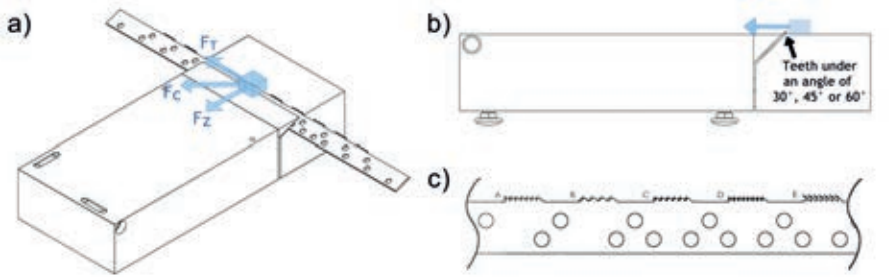

Figure 5: (a) 3D view of the gelatin and teeth test setup. (b) Side view of the setup. (c) Example of the teeth that have been evaluated. A gelatin sample (small blue block) was placed near the teeth, which were placed under an angle. Pulling the sample in the force directions FZ, FT and FC, (as also shown in Fig. 1) evaluated the gripping force the teeth had on the sample in that specific direction. Force-displacement measurements were performed with a tensile tester.

results. Not all teeth were measured in all force directions and under all combinations of conditions in order to keep the amount of measurements to a manageable number. A total of 194 measurements were performed in measurement sessions 1 through 4, with each measurement taking about 4 minutes.

Measurement Session 1) Gripping force at teeth of different geometry. With the goal of finding a well-performing tooth geometry, various teeth were assessed (Fig. 6, top). These teeth had a constant height of 1.0 mm, and were varied in wedge angle (range 20° and 60°, see teeth A, B, C, & I), curvature (linear or radius of 1.0 or 2.0 mm, see teeth E, F, & H), combinations of teeth (D & F) and blunt teeth (G). For this measurement session, the teeth were kept under a 45° angle with respect to the horizontal surface (Fig. 5b). This angle was the mid-range value around which a high gripping force was expected to be measured. Force direction F_Z was assessed. The total number of measurements performed was 54 (9 different tooth geometries * 6 measurements per geometry).

Measurement Session 2) Gripping force at teeth of different width and height. The results of measurement session 1 showed that tooth geometry D (Fig. 6, top), having a combination of two differently sized teeth, generated the highest maximum gripping force (for full results see Section 4.1). These teeth were redesigned to function in force direction FT by curving them in a 45° angle sideways (Fig. 6, bottom), and were varied in height (1.0, 1.5, & 2.0 mm). The teeth also varied in width by equally distributing their number (range 4 to 8) over a length of 10 mm. Both 'combined teeth' (e.g., Fig. 6, bottom, tooth geometry B) and 'singular teeth' (e.g., Fig. 6, bottom, tooth geometry A) were designed. Measurements were performed in force direction FC, while again keeping the teeth under a 45° angle with respect to the horizontal surface. Total number of measurements performed was 80 (10 types of tooth geometries * 8 measurements per geometry). Figure 6 (bottom) provides an overview of the 10 teeth that were tested in measurement session 2.

Measurement Session 3) Gripping force in all force directions. From measurement session 2, teeth F and J (Fig. 6, bottom) were found to have the highest mean maximum gripping force (F_{max}) in force direction F_C (for full results see Section 4.1). These teeth were further assessed in force directions F_T and F_Z, whilst still keeping their angle with respect to the horizontal surface at 45°. Total number of measurement performed was 24 (2 types of tooth geometries * 6 measurements per geometry * 2 force directions).

Measurement Session 4) Gripping force for different teeth angles with respect to the horizontal surface. Following measurement session 3, tooth geometry J (Fig. 6, bottom) was found to provide the highest gripping force (F_{max}). Having already quantified the teeth in all force directions at a 45° angle with respect to the horizontal surface (Fig. 5b),

this angle was varied to 30°, 45° and 60°. The maximum gripping force was measured in force directions FC and the inverse direction of FZ (i.e., –FZ). –FZ was used to quantify the force required to draw a gelatin sample over the teeth in their non-gripping direction, which is equivalent to drawing tissue into the morcellator tube in a clinical scenario. Total number of measurement performed was 36 (6 measurements * 2 force directions * 3 angles with respect to the horizontal surface).

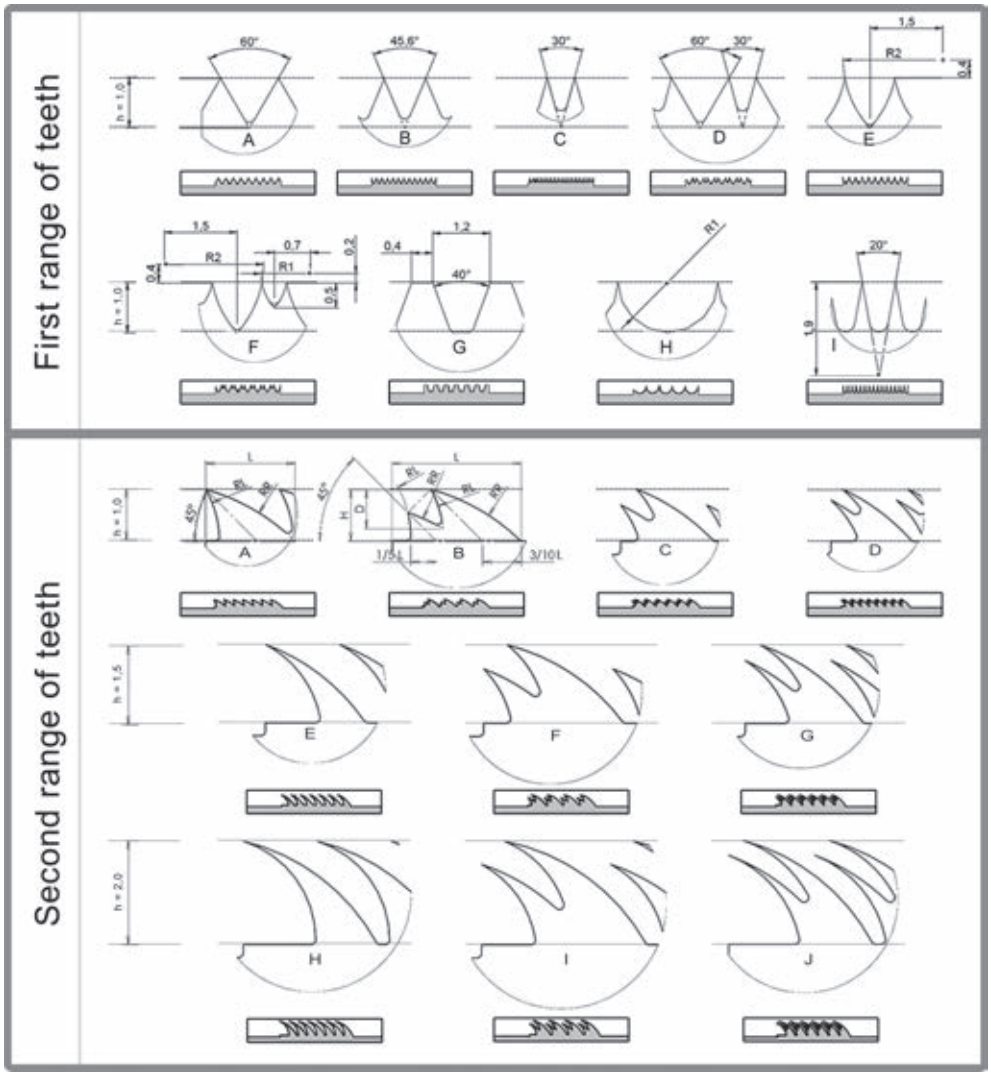

Figure 6: First (top) and second (bottom) range of teeth evaluated in measurement session 1 and sessions 2-4, respectively.

Teeth ring assessment for tissue grip – Bovine tissue tests

Through the design-oriented measurement sessions 1–4, tooth geometry J (teeth of 2.0 mm height and 1.4 mm width, 0.3 mm spacing between teeth, and a 45° angle with respect to the horizontal surface) was selected to be developed into a teeth ring (Fig. 7). This teeth ring was assessed in measurement sessions 5 and 6, in force directions F_T and F_Z respectively, using the test setup shown in Figure 8 and the same linear stage as used in sessions 1–4. Here, the teeth ring was attached to the end of a tube with outer diameter 12.5 mm and inner diameter 11.0 mm, which is approximately equal to the size of most current morcellation instruments. Bovine muscle tissue strips were collected from three larger tissue samples. The strips, each with size 10 x 10 x 40 mm, were cut in four different directions, assuring an equal distribution of muscle striations among all tissue samples. Each sample was clamped in the test setup by pulling it for a set distance into the fixation tube and placing a pin all the way through the tissue sample. The tissue strip was drawn into the morcellation tube and a 5 mm distance was kept between the fixation and morcellation tube.

Figure 7: Prototyped steel teeth ring, using tooth geometry J (Fig. 10, bottom), 2.0 mm height, 1.4 mm width, 0.3 mm spacing between teeth, and 45° inward angle. The ring has 21 teeth.

Measurement Session 5) Gripping force at tissue translation. Tissue placed inside the morcellation tube was pulled out of the tube by translating the fixation tube backwards over a distance of 12 mm. First, 9 measurements (i.e., 3 tissue strips, each used 3 times) were used to measure the friction resistance of the morcellation tube in the absence of gripping teeth. Next, 45 measurements (15 tissue strips, each used 3 times) were performed, measuring the maximum gripping force (Fmax) of the ring of teeth.

Measurement Session 6) Gripping force at tissue rotation. Lastly, tissue placed inside the morcellation tube was rotated by rotating the fixation tube by approximately 2.7 turns (by translating the linear stage over a distance of 107 mm). As in measurement session 5, first 9 measurements were performed without involving the gripping teeth to ascertain the friction resistance of the morcellation tube itself. Next, 60 measurements were performed, divided over 15 tissue strips, where each strip was measured 4 times. At each strip, the first three measurements involved rotating the tissue against the pointing direction of the teeth. During the fourth measurement, the tissue was rotated along with the pointing direction of the teeth, to measure the force required to rotate tissue free from the gripping teeth.

Differences between the tooth geometries were assessed using a one-way analysis of variance (ANOVA) with the Tukey-Kramer method and a significance level α of 0.05.

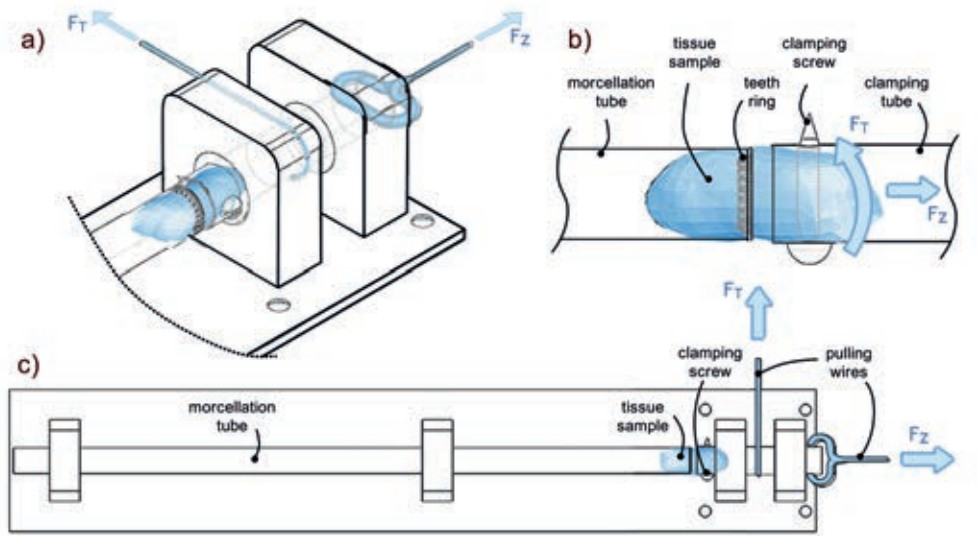

Figure 8: (a) 3D view of the bovine tissue and teeth test setup. (b) Close-up of tissue sample clamped and subjected to forces F_Z or F_T while in contact with the teeth ring. (c) Top view of the setup. A tissue sample (blue) is placed in contact with the teeth, which is mounted at the end of the morcellation tube. Pulling or rotating the sample in the force directions F_Z or F_T, as also shown in Figure 1, evaluates the grip the teeth have on the sample in that specific direction. Force-displacement measurements were performed with a tensile tester.

Results

Teeth optimization for tissue grip – Gelatin tests

An example of a force-displacement curve of a measurement where a block of gelatin was drawn into teeth D of teeth range 1 is shown in Figure 9a. At a displacement of 0 mm, the gelatin sample was right up against the teeth but not yet drawn into them. At continued displacement, the teeth dug into the sample and elastic deformation of the sample occurred while the measured force sharply rose. At the force peak (F_{max}), the sample material started to rupture. As a result, the teeth lost grip and the measured force dropped sharply. At continued displacement, the sample was drawn over and through the teeth, where the second rise and drop in grip force can be attributed to the teeth regaining their grip on the gelatin sample.

Measurement Session 1) Gripping force at teeth of different geometry. Means and standard deviations of F_{max} at all teeth of the first teeth range (Fig. 8, top), measured in force direction F_Z, are presented in Figure 9b. The ANOVA revealed a significant difference between tooth geometries, ($F(8,45) = 3.56$, $p = .003$). Teeth type D provided the highest mean F_{max}. This difference is statistically significant compared to teeth types A, B, G, H, and I ($p_{A\text{-}D} = .043$, $p_{B\text{-}D} = .022$, $p_{G\text{-}D} = .007$, $p_{H\text{-}D} = .001$, $p_{I\text{-}D} = .015$). A possible explanation why teeth type D outperforms the other teeth types may be that it uses a combination of two different teeth types (A and C). The depth of the teeth alternate among each other, which may have an effect on the location from where the gelatin sample starts to rupture.

Measurement Session 2) Gripping force at teeth of different width and height. Means and standard deviations of F_{max} for all teeth of the second teeth range (Fig. 8, bottom), measured in force direction F_C, are presented in Figure 9c. According to the ANOVA, the tooth geometries were significantly different from each other ($F(9,70) = 2.30$, $p = .025$). The two teeth types with the highest mean F_{max} were F and J, with 0.92 N (SD = 0.13 N) and 0.97 N (SD = 0.11 N) respectively. Only teeth J was statistically significantly different from teeth D ($p_{D\text{-}J} = .021$).

As the teeth height was varied between h = 1.0 mm, 1.5 mm and 2.0 mm, grouping those respective gripping forces together gave 0.70 N (SD = 0.31 N), 0.82 (SD = 0.23 N), and 0.91 N (SD = 0.12 N), respectively. According to the ANOVA, these three means were significantly different from each other, $F(2,77) = 5.19$, $p = .008$). The mean force for teeth with a height of 2.0 mm was statistically significantly higher compared to the mean force of teeth 1.0 mm in height ($p = .006$). No statistically significant difference was found for the teeth having a height of 1.5 mm as compared to the other teeth. The teeth providing the highest mean gripping force of both the 1.5 mm and 2.0 mm teeth height groups, being teeth F and J, were selected to be further investigated.

Measurement Session 3) Gripping force in all force directions. Measuring the gripping force of teeth types F and J in all force directions yielded the results as shown in Figure 9d. Teeth type J outperformed F in all measurements, although this difference is only statistically significant in direction F_T ($F(1,10) = 13.33$, $p = .004$).

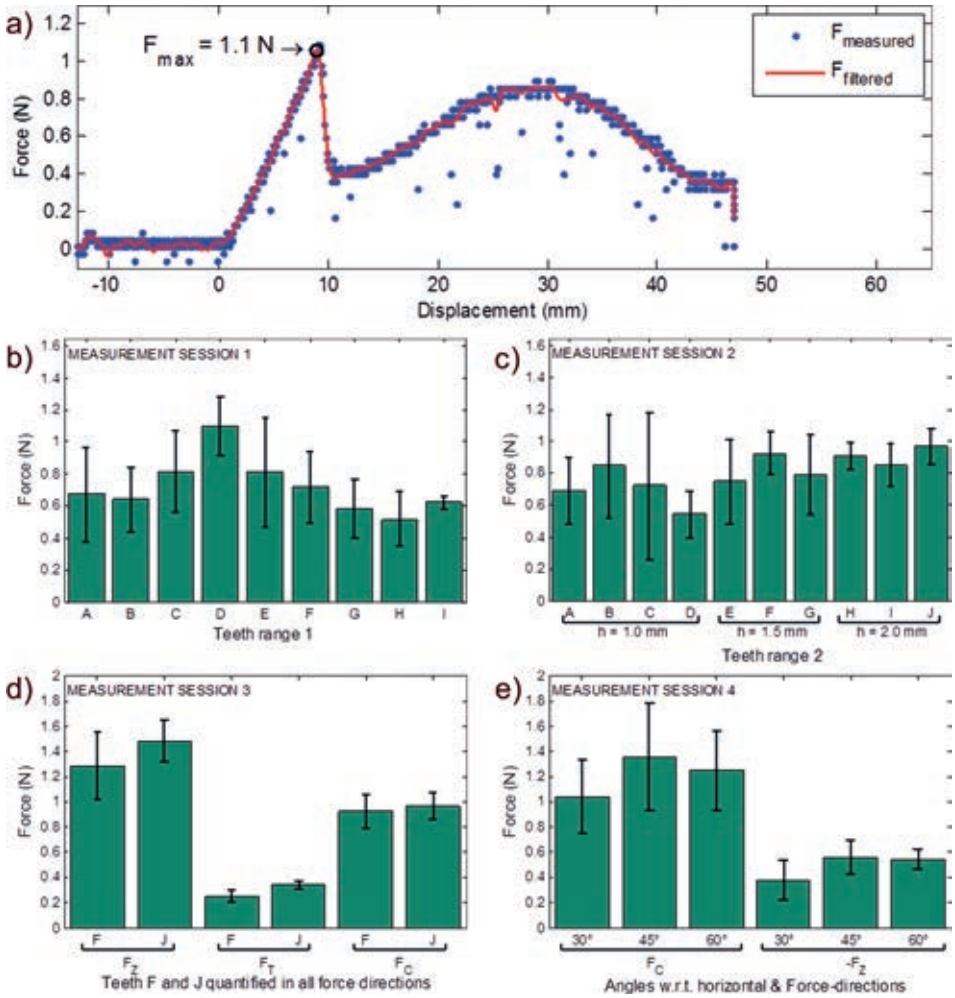

Figure 9: (a) Characteristic sample measurement (teeth range 1, teeth type D, measurement session 1). The maximum grip force on the gelatin sample is indicated by Fmax. (b–e) Results of measurement sessions 1 through 4. All results are presented as mean ± SD gripping force. (b) Measurement session 1. Force generated by various tooth geometries in force direction F_z. (c) Measurement session 2. Force generated by various geometry and size teeth in force direction F_c. (d) Measurement session 3. Force generated by teeth types F and J in force directions F_z, F_T and F_c. (e) Measurement session 4. Force generated by tooth geometry J in force directions F_c and inverse of F_z (i.e., F_z), each for three different angles of the teeth with respect to the horizontal surface.

Measurement Session 4) Gripping force for different teeth angles with respect to the horizontal surface. Measuring teeth type J (Fig. 9, bottom) while varying their angle with respect to the horizontal surface (Fig. 5b) resulted in Figure 9e. Force directions F_C and the reverse of F_Z (i.e., $-F_Z$) had been assessed. In the direction of $-F_Z$, the force should have been as low as possible, as this represents the resistance of the sample when drawing it along with the facing direction of the teeth, rather than opposing them. No statistically significant differences were observed. For the design of the teeth ring, the aim was to generate a gripping force in the direction of FC as high as possible. Accordingly, the choice for teeth type J under an angle of 45° was made.

Teeth ring assessment for tissue grip – Bovine tissue tests

Measurement Sessions 5&6) Gripping force at tissue translation and rotation.
Measurements were performed using bovine tissue, assessing the gripping force in force directions F_Z and F_T, by respectively translating and rotating tissue while in contact with

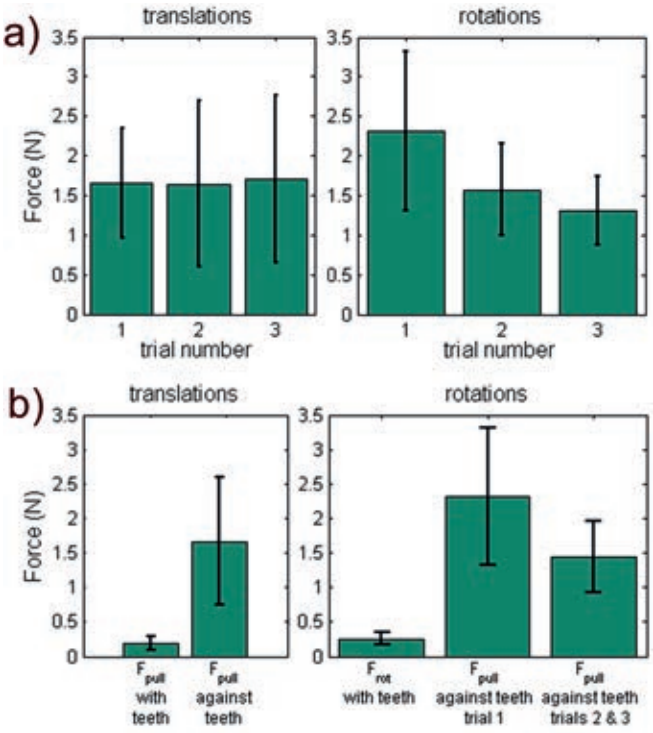

Figure 10: Results of measurement sessions 5 and 6. (a) Mean ± SD maximum teeth gripping force in force directions F_z and F_c (translations and rotations plot respectively). Three measurement trials were performed per tissue strip, and results are group per trial number. (b) Results of measurement sessions 5 and 6. Mean ± SD of the maximum teeth gripping force pulled along with and against the pointing direction of the teeth, respectively.

the teeth ring. The teeth ring was designed using teeth type J (see Fig. 6) under an inward angulation of 45° with respect to the morcellation tube. All tissue strips had been measured three times. Separating the measurements into groups based on their trial number yielded the results shown in Figure 10a. No significant differences were observed in the F_Z force direction. However, the ANOVA showed a significant difference between trials in the F_T force direction ($F(2,42) = 8.01$, $p = .001$) (see Fig. 10b). The gripping force for the first trial was significantly higher compared to subsequent trials ($p_{trial\ 1\ -\ trial\ 2} = .019$, $p_{trial\ 1\ -\ trial\ 3} = .001$), potentially a result of tissue damage caused by the teeth. In the force direction F_Z, all the data was therefore grouped. However, in the direction F_T the first time a tissue strip was measured was considered separately from subsequent trials.

The results for both force directions, measured both against and along with the teeth, are shown in Figure 10b.

Instrument design

The tests performed in measurement sessions 5 and 6 with the teeth ring yielded a maximum gripping force of 1.67 N (SD = 0.93 N) in the FZ direction, and 2.32 N (SD = 1.00 N) and 1.44 N (SD = 0.53 N) in the FT direction for the first and subsequent trials, respectively. Because existing morcellators vary in diameter, it is interesting to extrapolate these results [9]. Considering that the teeth ring had 21 teeth that were equally distributed along its inner diameter (øinner = 11.5 mm), a teeth ring integrated into a morcellator with an outer diameter of 15 mm and wall thickness 0.5 mm (leading to øinner = 14 mm) would have 25 teeth. Such a teeth ring would provide 2.76 N of gripping force in the FT force direction the first time that grip is generated (assuming that all teeth grip the tissue equally). Assuming that the gripping force is a linear function of the number of teeth, scaling up the diameter of the morcellation tube to 20 and 30 mm (thereby matching for example the 20 mm diameter of the Morce Power Plus (Richard Wolf, Germany)[81] and the 30 mm diameter of a proposed transvaginal morcellation design [82]) would provide 3.76 N and 5.74 N of grip force, respectively. The function that relates torque to radius (=*rF*) shows that for a tube of 15 mm diameter, a single teeth ring can counteract a torque up to 1.93 Ncm (=0.7 cm * 2.76 N). For diameters of 20 and 30 mm this would be 3.57 Ncm and 8.32 Ncm per teeth ring, respectively.

Torques of cutting blades reported in literature range from 80 Ncm (TCM3000BL Morcellator, Nouvag [83]) to 1.5 Nm (MoreSolution, Axtrocare [84]), whereas the RPM of morcellators ranges from 50 to 2,000 RPM (TCM3000BL Morcellator: 50 to 1000, MorseSolution: 100 to 800). Torque is inversely related to RPM, and thus morcellators

that allow for higher RPM have a lower maximum torque. The optimal torque-RPM setting likely depends on the tissue type, the diameter of the morcellation tube, and the pulling force (F_{pull}) with which the tissue is presented to the blade. Extrapolating the measured torque resistance for a single teeth ring to a series of stacked rings yields an estimated torque resistance of 38 Ncm, assuming 20 stacked rings over a length of 30 mm and a tube diameter of 15 mm (Fig. 3b). This torque resistance accounts for approximately half of the possible maximum torque generated by for example for the TCM3000BL Morcellator [83]. The gripping force generated by 20 stacked rings in the direction along with the teeth is estimated to be 4.7 N (0.2N * (25 teeth / 21 teeth) * 20 rings); hence the required pulling force (F_{pull}) to be supplied by the surgeon to the tissue mass only increases slightly. Although this is an approximate calculation, it does show that it is theoretically possible to use teeth to compensate for force F_T. A full concept design of a morcellator is provided in Figure 11. Future research should be conducted to experimentally validate the estimated torque resistances, and to integrate the stacked rings into an existing morcellation instrument.

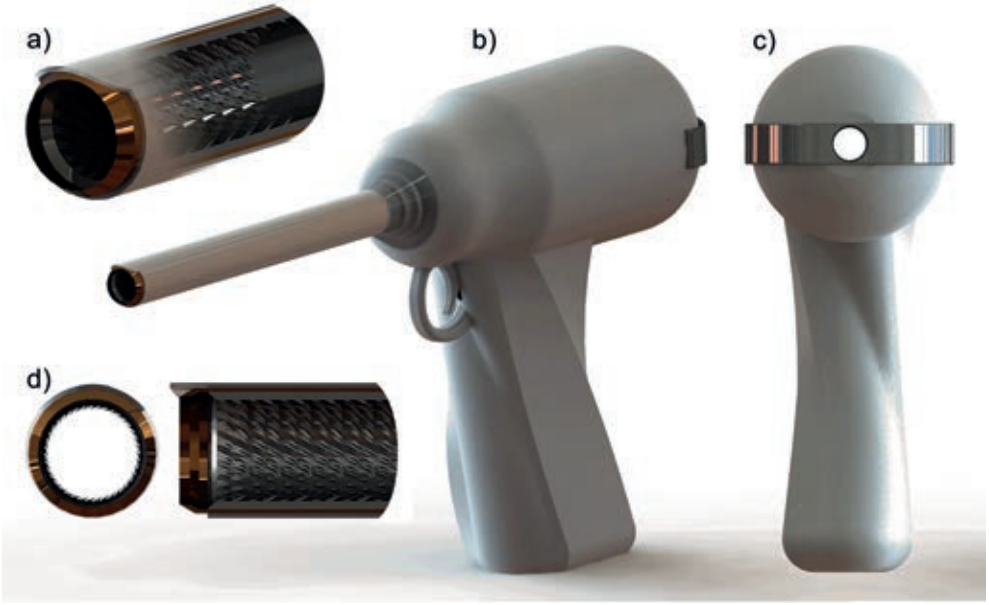

Figure 11: Concept design of a generic morcellator combined with an add-on module providing a passive inner morcellation tube with teeth rings that hook into the tissue strip at the occurrence of tissue mass spinning. (a) The add-on module connects to the morcellator through a clamping mechanism at the back-end. a) 3D zoom-in on instrument tip; (b) full 3D model (c) back view of model (d) front view and side view with cross-section of instrument tip.

Discussion

This paper presented the iterative design and evaluation of gripping teeth for the purpose of constraining tissue mass in the advent of its rotation along with the morcellation cutting blade. The measurements suggest that a series of stacked teeth rings can provide an adequate torque resistance for this purpose. Several measurement and design limitation have to be considered, however.

Measurement limitations

Measurement sessions 1 through 4 used porcine gelatin samples to evaluate the gripping strength of teeth of varying geometry, and empirically determine which geometry performed the best. The use of gelatin was advantageous as it allowed for a large number of measurements within a short time frame, was readily available, and had an elasticity modulus comparable to that of actual tissue. Gelatin is frequently used for needle-tissue interaction investigations and its force-position curve is linear. In contrast, bovine tissue is nonlinear and has a rupture toughness that differs from gelatin [85]. Therefore, the results from measurement sessions 1 through 4 have to be assessed relative to each other and should not be compared with sessions 5 and 6 in absolute terms.

Bovine muscle tissue is striated by nature, whereas the female uterus consists of smooth muscle tissue. Human uterine tissue or smooth muscle tissue that resembles the human uterus, are not readily available for testing. For this reason, measured gripping force levels may be different from a true clinical scenario. In our research, the tissue strips were cut in various directions to obtain a roughly equal distribution in striation directions, thereby compensating for the influence of striations. An additional limitation of the measurements was that the tissue strips were precut. Therefore, the shape of morcellated tissue strips created during clinical procedures was not a factor that influenced our results. Lastly, the measurement results represent a quasi-static scenario, because the tissue was slowly drawn through the teeth. The speed of tissue translation or rotation was not varied.

Not all observed differences in teeth gripping forces were statistically significant at each individual measurement session. However, through the successive design process (Fig. 4), this research iterated towards a single teeth design. This process was an efficient alternative to testing all teeth across all possible variations, angles, and force directions. The current design, however, may represent a local optimum in the design solution space, and further refinements may be possible.

Teeth design

The measurement results in this research were used to come to a teeth design that provided the largest gripping force in specific force directions. These teeth were subsequently integrated into a proof-of-principle design for future validation and quantification.

The measurements were not intended to provide a deep understanding of the relation between tooth parameters (e.g., geometry and sharpness), tissue properties (e.g., elasticity and viscosity), or crack formation. Although the ability to grasp tissues (e.g., the gall bladder or colon) with laparoscopic graspers without causing tissue damage is important for clinical practice [86], the amount of published research into the design of gripping teeth with respect to pinching force, tissue damage, and tissue slippage is limited [86-91]. One factor of importance is the curvature of individual teeth, where an increase of radius results in reduced tissue damage at the expense of gripping strength [87-90]. During morcellation the degree of tissue damage is not important; hence in this research only aggressive teeth were assessed. In the literature, both 1.0 mm and 2.0 mm sized teeth have been tested, resulting in no clear differences in gripping forces between these two designs [88, 89]. This is in agreement with the present results (Fig. 9c). However, the results in the literature have been obtained for straight symmetrical teeth, comparable to the teeth tested in measurement session 1 (Fig. 10, top). To the best of our knowledge, no results are available in the literature with respect to angled teeth such as those used in measurement sessions 2, 3 and 4 (Fig. 8, bottom).

An interesting finding was that the best-performing tooth geometry consisted of two different sized teeth (teeth D, Fig. 8, top). Compared to a single teeth design (e.g., teeth A, Fig. 8, top), there may be a difference in crack formation and propagation, because the depths with which the tissue can sink in between the teeth alternate between 0.85 mm and 0.65 mm. However, teeth F (Fig. 8, top) also consisted of two differently sized teeth, yet did not exhibit the same performance as teeth D. The underlying mechanism behind the effects of alternating teeth requires further investigation.

The design of the teeth is a trade-off between gripping forces in the F_T and F_Z force directions and the obstruction force $-F_Z$. These forces are a function of teeth size, tooth geometry, number of teeth, and their angle with respect to the horizontal surface. When stacking multiple teeth rings in a row, the relative spacing between the rings will be another factor that determines the amount of tissue grip generated. One can make a comparison in this regards to fenestrations (i.e., openings) in laparoscopic graspers, where it has been theorized that fenestrations allow the tissue to bulge into them, thereby achieving a form-fit between tissue and grasper. Literature provides

contradicting evidence regarding the effects of fenestrations for creating tissue grip [89,91], thus providing no indication regarding the distance that teeth need be apart.

Lastly, the structural integrity of the tissue strip is of importance for the level of gripping force that can be obtained with the teeth. This is evidenced by the difference that was observed in the F_T force direction between the first and subsequent trials. This finding suggests that the initial gripping force generated on tissue mass at the onset of tissue mass rotation should directly be of adequate level to prevent the mass from spinning.

Instrument design and optimization

In essence, by using teeth to prevent the tissue mass from spinning, one is removing the surgeon from the 'force loop' near the cutting blade. In the standard morcellator design, the influence of the surgeon is limited to applying a pulling force F_{pull}, whereas in order to prevent the tissue mass from spinning, the surgeon should also be able to rotationally constrain the tissue mass. It is possible, but impractical, to leave this to an assisting surgeon who makes use of a laparoscopic grasper disposed through a different trocar. By integrating gripping teeth designed to compensate for force F_T whilst not hindering tissue strip cutting and transport, the tissue mass is controlled without actually having to change the standard morcellation process. Moreover, by preventing the tissue mass from spinning, the amount of tissue spread generated should be reduced. The degree in which tissue spread decreases as well as potential influences of this method on the human-machine interaction (e.g., the influence of increased pull force) are subjects for future research.

Integrating the teeth into an existing morcellator introduces certain design complexities considering that stacked teeth rings need to be integrated into the morcellation tube (Fig. 3b). A potentially simple fabrication method is to punch press the teeth into a single piece of sheet metal and bend this sheet metal into a tube shape. To be considered is that the addition of a teeth-bearing tube placed into an existing morcellation tube reduces that instrument's inner diameter. Preferably, the cutting tube should flare open to a larger diameter, allowing for the insertion of a tube with an inner diameter equal to the effective cutting blade diameter. The LiNA Xcise for example has this feature [92].

The presented instrument design (Fig. 11) may be extended to further improve tissue mass control. Going back to both the cookie cutter shark and the lamprey, their use of a suctorial mouth may inspire continued morcellator development. As suggested in several patents [29,32,64], the use of suction to draw tissue into contact with the morcellation instrument, combined with a fluid environment, may be an effective strategy. In light of the recent implementation of laparoscopic containment bags that

catch the tissue spread [47,59-61], adding integrated teeth and suction may be a complementary solution to improve morcellation efficacy and safety.

Conclusions

Through an iterative design and measurement process, a teeth ring was designed, prototyped, and evaluated with respect to its potential gripping strength on tissue. The evaluation showed that the teeth ring generated grip in the advent of tissue translation and rotation. Stacked teeth rings over a length of 30 mm and having an inner tube diameter of 15 mm provide a theoretical 38 Ncm of torque resistance to prevent the tissue mass from rotating along with the morcellation cutting blade. Future research may implement the proposed design into an already existing morcellator and assess it through an in-vitro benchtop evaluation.

Acknowledgments

The authors would like to thank Menno Lageweg and Remi van Starkenburg for their help in fabricating the test facilities and the teeth ring.

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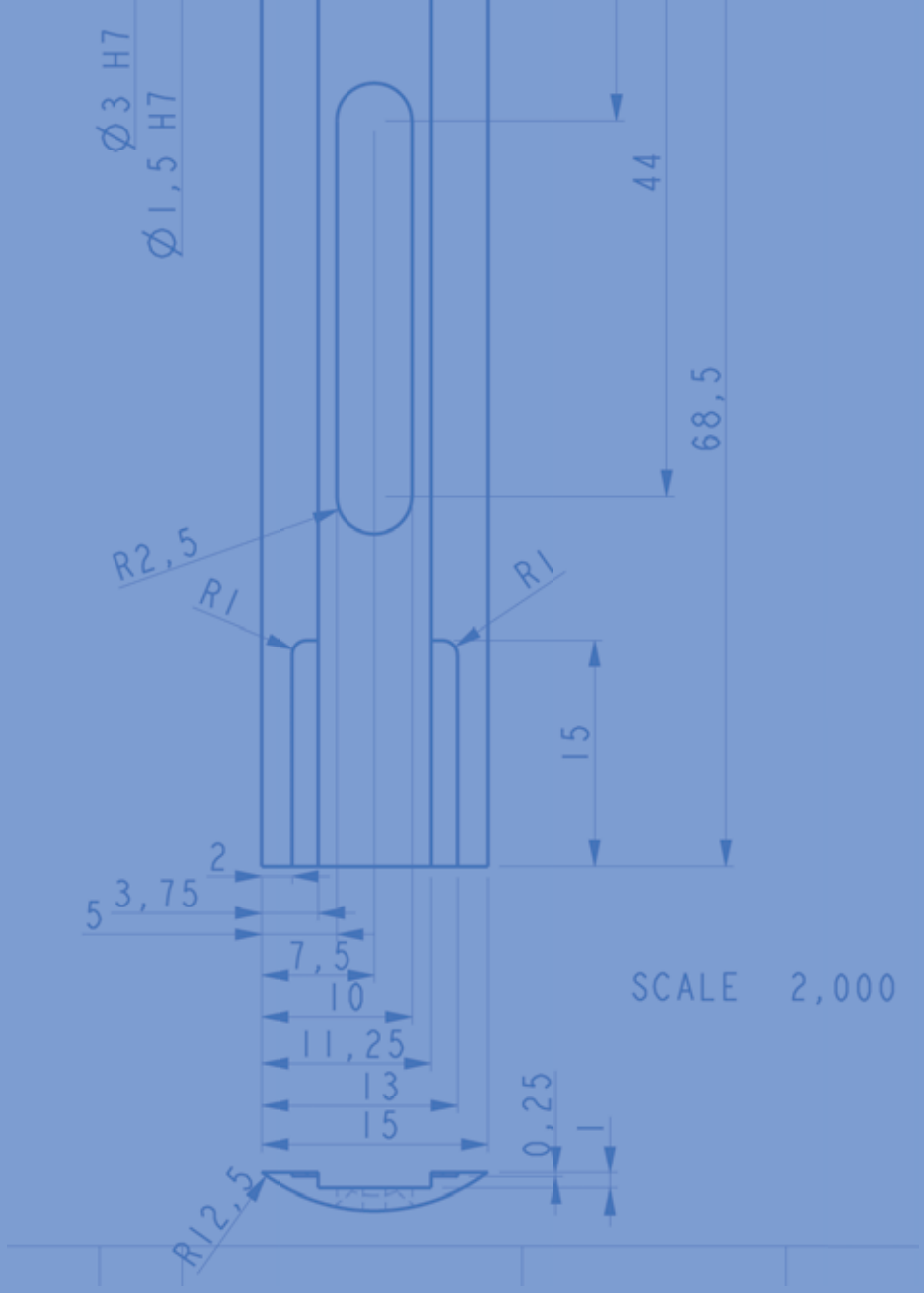
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Incidence and groups at risk for unexpected uterine leiomyosarcoma: A Dutch nationwide cohort study

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8

Accepted *Archives of Gynecology and Obstetrics*

Abstract

Objective: To estimate the risk of uterine leiomyosarcoma in patients undergoing gynecological surgery. Also, to identify groups at risk for unrecognized uterine leiomyosarcoma

Methods: A national cohort study was performed evaluating all uterine leiomyosarcoma (ULMS) diagnosed in the Netherlands between January 2000 and September 2015. Cases were identified and supplied by the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). Unexpected and expected ULMS were compared. Approval for this study was granted by the Medical Ethics Committee of all participating hospitals and by the review board of PALGA.

Results: 262 original cases were included. The overall incidence of ULMS in our study was 0.25% or 1:400 patients. The incidence of unexpected ULMS was 0.12% or 1:865 patients. Preoperatively, a malignancy was unexpected in 46% of the cases and expected in 54%. Abnormal uterine bleeding constituted most of the symptoms. 90% of women underwent abdominal hysterectomy and/or bilateral salpingo-oophorectomy .

Conclusions: Leiomyosarcoma are rare. Woman aged 40-50 years with abnormal uterine bleeding are most at risk for unexpected ULMS. In contrast this risk is low in postmenopausal women. ULMS were highly uncommon in women aged under 40 years.

Keywords
Hysterectomy; laparoscopy; leiomyosarcoma; morcellation.

Introduction

The number of laparoscopic procedures has decreased in favor of laparotomy, since the Food and Drug Administrations (FDA) decided to discourage power morcellation [1-5] This decision was based on the occurrence of unexpected uterine (leiomyo)sarcoma during hysterectomy or myomectomy for presumed benign fibroids. It was calculated by the FDA that this risk is as high as 1 in 498 for uterine leiomyosarcoma (ULMS).[6] However, the evidence that formed the basis for this calculation has been criticized for its weakness and potential bias. For instance, mainly single center studies were used and pre-operatively diagnosed malignancies were included. [7,8] Recently the FDA has updated this risk of occult ULMS to 1 in 495 to 1 in 1100 women undergoing surgery, using data from more recent studies.[9] Applying this notable range to a decision analysis for perioperative risk estimations regarding laparoscopic hysterectomy versus laparotomy, scenarios can be found in favor for both approaches.[10] To improve the accuracy of such models and thus better inform patients, more data on the actual incidence of (unexpected) ULMS is needed. The primary aim of our study was to expand the current data by calculating the risk of unexpected ULMS during gynecological procedures in The Netherlands. Secondly, we attempted to identify groups at relatively high or low risk for ULMS to enhance the pre-operative selection for the proper surgical procedure of these patients.

Methods & Materials

Approval for this study was granted by the Medical Ethics Committee of all participating hospitals and by the review board of PALGA.

A national cohort study was performed evaluating all patients diagnosed with ULMS in the Netherlands between January 2000 and September 2015. Cases were identified and supplied by the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA).[11] Women with a histo-pathologically confirmed ULMS diagnosis after surgical treatment (abdominal, vaginal and laparoscopic hysterectomy; hysteroscopic, laparoscopic and abdominal myomectomy; staging laparotomy and debulking surgery) were included. Only the initial procedure identifying the ULMS was considered, to avoid multiple registration of the same case. This naturally implies that second opinions of these cases, although registrered in the PALGA database, were excluded. Basic patient characteristics, relevant medical history, clinical presentation and the preoperative diagnostics were retrieved from medical charts. All abnormal bleeding patterns (including excessive , irregulair or postmenopausal) were defined as abnormal uterine bleeding. Size of myoma was measured in centimeters or compared to

weeks of gestation. Rapid growth of myoma was considered present if this was explicitly stated in the medical charts. Cases were classified as unexpected ULMS if (any type of) malignancy was not considered preoperatively, was not stated as indication for surgery, or if surgical techniques were used that were not in accordance with ULMS treatment guidelines (meaning abdominal hysterectomy, with or without salpingo-oophorectomy) . Preoperative ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), hysteroscopy and endometrial sampling/curettage was considered suspicious if (any type of) malignancy was considered by the examining gynecologist, radiologist or pathologist. To calculate the risk of ULMS in surgical specimens in our cohort, the number of all types of benign tumors of the myometrium was used during the same inclusion period. This number was also derived from the PALGA database and consisted of leiomyoma (epithelioid, myxoid, cellular, bizar, angioleiomyoma, angiomyoleiomoma), angiomyofibroblastoma and inflammatory pseudotumors. An independent student-t test, a Pearson Chi square test and Fisher exact test were used where applicable. Differences with a p-value <.05 were considered statistically significant. SPSS 20 was used to analyze all data.

To compare our data, a literature search was performed using the PubMed, Web of Science, Embase and Cochrane databases. Search terms consisted of 'hysterectomy', 'myomectomy ', 'uterine (leiomyo)sarcoma', 'risk', 'prevalence' and 'incidence'. Only original cohorts from multicenter studies evaluating ULMS were included, to match our cohort as well as possible.

Results

From January 2000 until September 2015, 752 ULMS were registered in The Netherlands by the PALGA database, originating from 67 hospitals. 43 hospitals (63%) were willing to participate in this study, comprising of 6 academic referral centers (of 8 in total), 2 additional tertiary referral centers (of 2), and 35 general hospitals (of 57). These hospitals reflect 514 cases (72%). 252 cases were excluded because they were not original cases (mainly second opinion referrals to specialised pathology centres to confirm the diagnosis) or due to not meeting the inclusion criteria.(figure 1) In all, 262 original cases were eligible for inclusion. Of these, the medical records were missing from 26 cases and only the original pathology report could be found. These cases were therefore only used to calculate the risk of ULMS and not for patient characteristics.

Basic characteristics are shown in table 1. Of the cases of ULMS, 54% were suspected of having a malignancy and 46% were unexpected. The mean age in the expected group was 62 (range 20-91) and it was 52 (range 31-81) in the unexpected group. ULMS was most often found in women aged 50-60 years as is demonstrated by the

age distribution in figure 2. Sixty-seven percent of the unexpected cases concerned pre-menopausal women and 17% of the expected cases were pre-menopausal. Abnormal uterine bleeding (AUB) constituted most of the symptoms: 43% overall and 52% versus 33% in the unexpected and expected group.

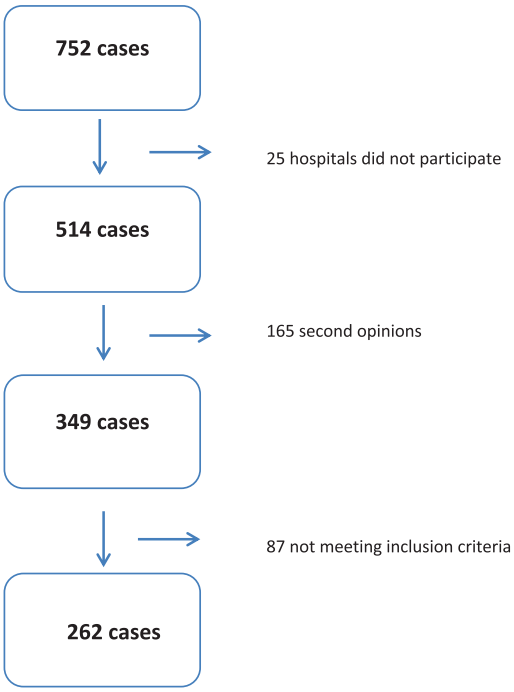

Figure 1: Inclusion flowchart. 25 hospitals did not participate, in the majority of instances without reason.Second opinions consisted of double registrations in the PALGA system. Only the first original case was included in this study. Not meeting inclusion criteria: 14 stromal tumors of unknown significance (STUMP), 5 endometrial stromal sarcoma (ESS), 4 carcinosarcoma, 2 adenosarcoma, 1 malignant mixed müllarian tumor, 1 undifferentiated endometrial carcinoma, 2 cellular leiomyoma, 43 other reasons (non-gynecological sarcomatoid tumors or recurrences of primary tumors not eligible for inclusion), and from 15 cases no chart could be found.

The pre-operative average uterine size was in accordance with 20 weeks of gestation (based on 82 cases) and pre-operative average myoma size was 10cm (based on 139 cases). Uterus and myoma were larger in the expected ULMS group: 19 weeks versus 22 weeks, p .01 and 9cm vs 12cm, p .003. For the majority of cases (64%) the myoma was solitary (based on 137 cases). In cases with multiple myoma, a malignancy was less often expected: 34%, $p < .06$. Rapid myoma growth was reported in 67% of cases (based on 42 cases). No differences were found regarding growth and menopausal status or expected versus unexpected ULMS.

Table 1: Basic characteristics

		Cohort	Unexpected	Expected
N		**236**	**109 (46%)**	**127 (54%)**
Age		**58 (12, 20-91)**	**52 (9, 31-81)***	**62 (12, 20-91)***
Menopause	Pre	40	67*	17*
	Post	60	33*	83*
Symptoms	Pain	15	14	16
	AUB	43	52	33
	AUB + pain	12	12	12
	Mass effect	21	20	22
	Weight loss	8	0	15
	None	2	2	2
Type of Surgery	AH	25	46	5
	AH+BSO	46	30	65
	LH	4	7	2
	VH	1	3	0
	MM	2	4	0
	TCRM	4	7	1
	Debulking	13	1	26
	Other	5	3	1
No of Myoma	One	64	57	72
	> one	36	43	28
Uterine Size[a]		20	19*	22*
Myoma Size[b]		10	9*	12*
Rapid myoma growth	No	33	44	18
	Yes	67	56	82

Age: mean (standard deviation, range); Expected/Symptoms/Type of Surgery: percentages. AUB: abnormal uterine bleeding; AH: abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; LH: laparoscopic hysterectomy; VH: vaginal hysterectomy; MM: myomectomy; TCRM: transcervical resection of myoma. Uterine size based on 82 cases, Myoma size based on 139 cases. Rapid myoma growth based on 42 cases. *: significant at $p \leq .05$

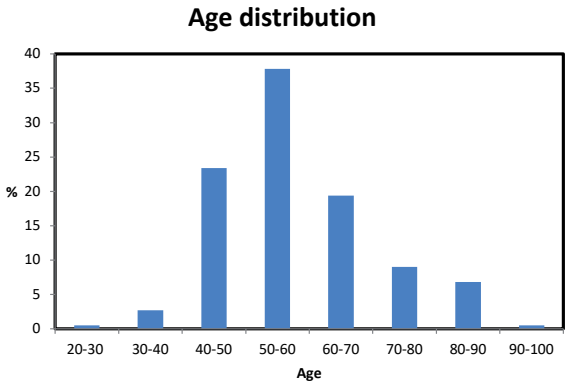

Fig 2: age distribution of our cohort (%)

Next, the pre-operative workup and treatment is presented. Nearly all patients (99%) received an US. CT and MRI were performed in 29% and 7% of cases respectively, hysteroscopy in 16% and sampling of the endometrium in 38%. For US, CT, MRI, hysteroscopy and sampling respectively, 37%, 75%, 56%, 32% and 45% of the findings were indicative of a malignancy. (table 2) US and sampling were more often suspicious in postmenopausal patients than in premenopausal patients (51% versus 20%, p < .001 and 58% versus 17%, p <.001 respectively).

Table 2: Pre-operative diagnostic workup.

		Cohort (N=236)	Premenopausal	Postmenopausal
Ultrasound	Total	99	98	99
	Suspicious	37	20*	51*
CT	Total	29	19	36
	Suspicious	75	71	76
MRI	Total	7	7	7
	Suspicious	56	43	67
Hysteroscopy	Total	16	13	29
	Suspicious	32	18	39
Endometrial Sampling	Total	38	32	44
	Suspicious	45	17*	57*

Numbers are percentages of the cohort. *: significant at p ≤ .05

Most women (69%) were treated by abdominal hysterectomy with or without bilateral salpingo-oophorectomy (AH±BSO). An additional 15% of women received staging laparotomy or debulking surgery. Laparoscopic hysterectomy (LH) was used in only in 4% of all women. In the unexpected group, power morcellation was used in 2 cases. In addition, manual morcellation was performed in 2 other cases: to accommodate vaginal extraction of the uterus after LH, and during conversion of vaginal hysterectomy (VH) to AH.

During the same inclusion period as our cohort, 144.431 benign tumors of the myometrium were registered by PALGA. Consequently, the overall incidence of ULMS in our study was .25% or 1:400 patients. The risk of unexpected ULMS was .12% or 1:865 patients. The risk of receiving other treatment for ULMS than AH±BSO or staging/ debulking in the unexpected group was .04% or 1:2500 patients.

Discussion

This nationwide cohort study evaluated all ULMS cases in the Netherlands from January 2000 – September 2015. The risk of encountering an unexpected ULMS was 0.12% or 1:865 patients. Moreover the risk for patients with ULMS to undergo surgical treatment other than AH± BSO, staging or debulking was .04% or 1:2500 patients. These numbers are in concurrence with the studies found in our literature search. In total, 7 multicenter cohorts were found, with incidences ranging from 2.3% or 1:44 to .07% or 1:1465 cases [12-18] (table 3) Unfortunately, a meta-analysis of the data from these studies could not be performed due to heterogeneity of the included study population.

Based on our evaluation, certain groups are at higher risk for preoperatively unrecognized ULMS than others. First, women aged 40 years and younger constituted only 4% of our cohort. Therefore minimally invasive and/or fertility sparing treatments such as a laparoscopic myomectomy could be considered for these women. The highest risk for preoperatively unrecognized ULMS was found in women aged 40-50. In this age group a malignancy was suspected in only 15% of the women as opposed to 53% and 63% in women aged 50-60 and 60-70 respectively. In women over 70 years of age, a malignancy was suspected in over 80%. Furthermore, symptoms and preoperative workup were not distinctive for this high-risk group. In our cohort most premenopausal women complained of AUB and, in contrast to post-menopausal women, this usually does not indicate a malignancy. Furthermore, as AUB and fibroids are the main indication for hysterectomy in benign conditions these women are likely to undergo surgery.[19]

Next, a significant difference was found between uterus size and myoma size in unexpected and expected cases. Yet, these differences were small and size was overall large in both groups. Furthermore, these results should be interpreted with caution because possibly only distinctive cases were well registered.

Finally, it was found that preoperative diagnostics were less likely to diagnose a malignancy in our cohort of premenopausal women. For instance, endometrial sampling demonstrated a malignancy in 57% of postmenopausal women compared to only in 17% of premenopausal women. Although US is often a readily available diagnostic test, the diagnostic value in our cohort was low. Interestingly an evaluation of tumor vascularity and Doppler measurements were not performed but in a few cases, although this could be due to suboptimal reporting and due to the time-span of the cohort. These measurements should not be overlooked as meanwhile favorable numbers regarding sensitivity, specificity and positive predictive value for ULMS have been described.[20] The vast majority of CT imaging (89%) was reserved for women over 50 years of age.

Table 3: Multicenter original cohort studies.[11-17]

Author	Study	Period	Origin	Population	ULMS risk
Skorstad et al. 2016	Retrospective nationwide cohort	2000-2012	Cancer Registry of Norway	Women undergoing laparoscopy due to abnormal uterine bleeding or leiomyoma	.08% / 1:1250
Oduyebo et al. 2016	Retrospective case controlled	Jan 2005-Aug 2012	Brigham and Women's Hospital & Dana-Farber Cancer Institute	Women undergoing myomectomy or hysterectomy via robot or laparoscopy with electromechanical or manual morcellation	.19% / 1:526
Rodriguez et al. 2016	Retrospective cohort	2002-2011	Clinformatics DataMart database	Women aged 25-64 with leiomyoma undergoing laparoscopic supracervical hysterectomy or myomectomy	.14% / 1:714
Raine-Bennett et al. 2015	Retrospective population based cohort	2006-2013	Kaiser Permanente's electronic health record and regional claims systems	Women over 18 years undergoing hysterectomy for leiomyoma	.23% / 1:429
Raspagliesi et al. 2017	Retrospective cohort	2004-2014	8 health centers of the MITO group	Women over 18 years undergoing surgery for leiomyoma	2.3% / 1:44
Nugent et al. 2015	Retrospective cohort	2000-2014	German multi-centers group (VAAO) + 2 additional hospitals	Women with AUB, fibroids and/or pain undergoing LSH or LM	.07% / 1:1465
Parker et al. 1994	Retrospective cohort	1988-1992	Santa Monica Hospital and St. John's Hospital. California	All women undergoing surgery for leiomyoma	.08% / 1:1250
van den Haak et al. 2017	Retrospective cohort	Jan 2000 – Sept 2015	PALGA nationale database	All women with pathology confirmed ULMS and surgical treatment	.12% / 1:865

Naturally, in this group malignancies were more often suspected and CT was used to confirm the suspicion raised by a patients history, or to aid in staging of the disease. However, in light of the aforementioned risk group it is interesting to notice that in women aged 40-50, a CT and MRI was performed in a minority of cases. One explanation may be that these women were previously not considered at risk for ULMS. An increased awareness may thus aid in reducing the number of unexpected ULMS in this group.

Our study has some potential weaknesses. Not all institutes were willing to participate, therefore not all cases could be verified. Next, due to the retrospective design, missing data occurred. A surprisingly low number of patients were treated by minimally invasive surgical treatments, explaining the very low risk for patients with unexpected ULMS to undergo non-standard oncological treatments. Therefore, this risk (1:2500) may have limited external validity. The strength of our study is the nationwide cohort. Almost all tertiary care academic centers as well as the majority of general care hospitals in the Netherlands participated in this study. In our literature search, only 1 other study encompasses true nationwide data.[12] This study consisted of women undergoing laparoscopy for abnormal uterine bleeding or leiomyoma. Our study evaluated all ULMS cases, eliminating selection bias due to treatment groups. Therefore notwithstanding the shortcomings, our data are a valuable addition to the already existing evidence. Furthermore our study identified high and low risk groups, thereby offering an additional means in clinical practice to decide a treatment strategy together with the patient. Future studies include a matched case-control study using this cohort, to further define risk factors for ULMS, although it will take some time to find proper matched cases. Also, given the increase in laparoscopic procedures in the past decade it will be of interest to analyse a more recent cohort to compare the number of expected versus unexpected cases and the number of patients who received suboptimal surgical treatment.

Conclusion

The risk of ULMS is overall low and the majority of cases were expected. Woman aged 40-50 years with AUB are most at risk for unexpected malignancies. ULMS were highly uncommon in women aged under 40 years.

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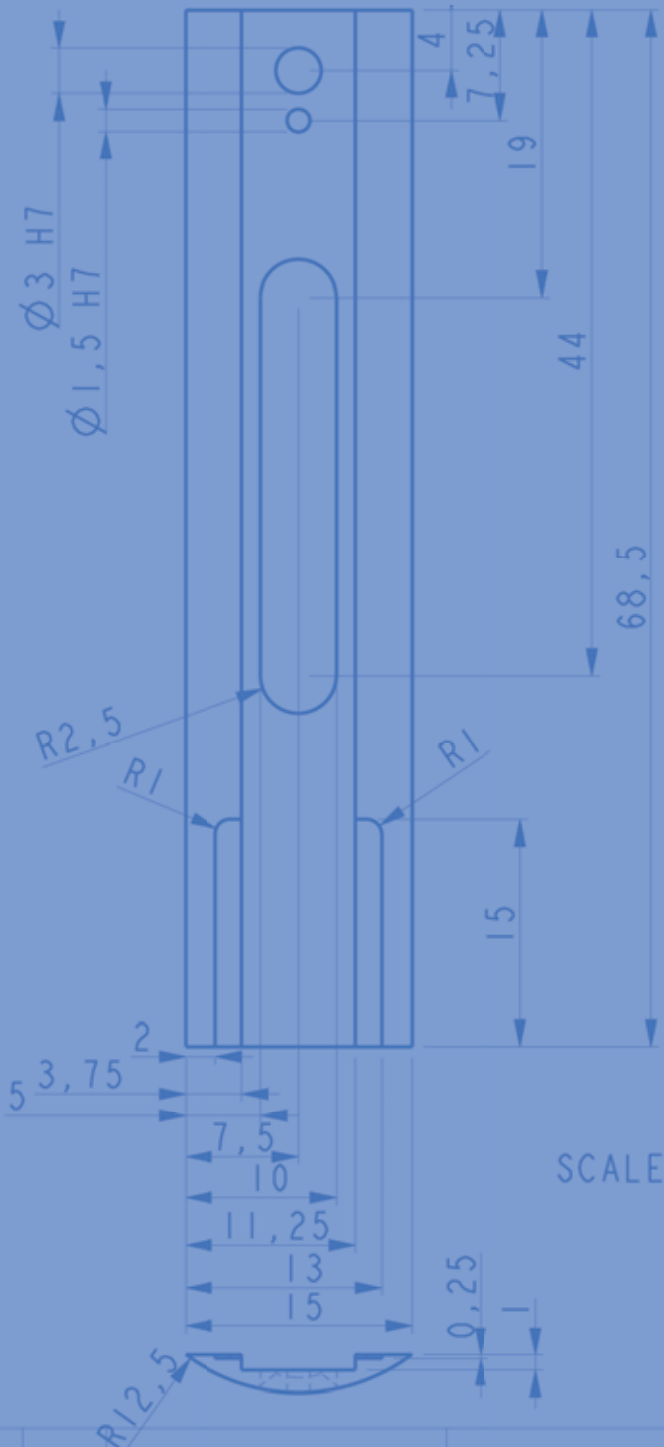
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Disseminated leiomyoma cells can be identified following conventional myomectomy

E.M. Sandberg, L. van den Haak, T. Bosse, F.W. Jansen

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BJOG. 2016 Dec;123(13):2183-2187

Abstract

Objective: Uncontained morcellation of leiomyomas during laparoscopic surgery has recently been discouraged, as undetected malignant tumours, namely leiomyosarcomas, could be fragmented which may result in upstaged disease. However, enucleating leiomyomas per se may be inappropriate from an oncological perspective because complete, radical resection of malignant tumours to prevent further tumour growth or recurrence is not achieved. Thus, the aim of this study was to determine whether spillage of leiomyoma cells occurs during laparotomic myomectomy.

Design: Observational study

Setting: Tertiary academic centre in the Netherlands.

Population: Women undergoing laparotomic myomectomy were included in the study.

Methods: Peritoneal abdominal washings were obtained on two occasions during the myomectomy procedure; the first one immediately after opening the abdomen and the second one after resection of the leiomyoma(s). Cytological evaluation of the fluids was performed.

Main outcome measures: The presence of leiomyoma cells in any of the washings.

Results: Five patients were included in this pilot study. All first washings were negative for leiomyoma cells. However, cytology positive for the presence of leiomyoma cells was found in three of the five second, post-myomectomy washings.

Conclusion: Tissue spillage from leiomyoma(s) occurs during conventional open myomectomy. The clinical relevance of tissue dissemination after myomectomy is unclear but it cannot be excluded that this may negatively affect the patient's outcome if there is malignant change within the enucleated leiomyoma(s). Therefore, it is questionable whether morcellation in specially designed containment bags after laparoscopic myomectomy, guarantees any additional oncological safety.

Introduction

The introduction of power morcellation in the field of gynaecology has contributed to the wider implementation of minimally invasive surgery by enabling laparoscopic extraction of large specimens. Although warnings regarding its oncological safety were published more than a decade ago[1,2], it was only in 2014 that the Food and Drug Administration (FDA) issued a press release discouraging the use of morcellation during laparoscopic gynaecologic surgery, namely hysterectomy and myomectomy, in the presence of leiomyomas.[3] This FDA statement was issued in response to reports of cases of morcellation of presumed benign tumours that subsequently turned out to be leiomyosarcoma(s). This in turn led to concerns that tissue dissemination of occult malignancy after morcellation could lead to an upstage of the disease.[4] Furthermore, preoperative prediction of malignant change within leiomyomas is unreliable in the absence of prognostic patient characteristics or discriminatory diagnostic tests.

One of the basic principles of surgical oncology is that malignant tumours should always be resected radically and in toto to prevent further tumour growth and/or recurrence. If all malignant tissue spillage is considered potentially harmful, as many authors advocate,[4-6] it can be questioned whether, from an oncological point of view, myomectomy for presumed leiomyomas is safe altogether. Indeed, the cleavage plane is almost never radical during myomectomy, regardless of the type of approach. Furthermore, leiomyosarcomas are heterogeneous tumours, meaning that malignant cells could be located anywhere inside the growth.

In light of these considerations we hypothesised that dissemination of leiomyomatous tissue occurs during resection of leiomyomas and not just as a result of subsequent morcellation of extracted tissue. Therefore the aim of the current study was to detect the presence of leiomyoma spillage during laparotomic myomectomy by performing peritoneal washings.

Methods

During the study period, all patients undergoing abdominal myomectomy at the Leiden University Medical Centre (Leiden, the Netherlands) were asked to participate. The study was exempted from Institutional Review Board approval, but patients were informed about the study procedure and gave oral consent. Inclusion criteria were women of 18 years or older, diagnosed with symptomatic leiomyomas and eligible to undergo abdominal myomectomy as per the judgment of the surgeon. Exclusion criteria were suspected malignancy and inability to give consent.

The abdominal myomectomy procedure was performed according to standard techniques. As part of the study, the entire abdomen was washed two times with 500 ml of normal saline during the procedure: the first washing was performed as a control, immediately after opening the abdomen, and the second washing after resection of the leiomyoma(s). After every washing the abdominal fluid was completely aspirated and collected in two separate bags for cytological evaluation. The main outcome of the study was to evaluate the presence of leiomyoma cells in any of the washings.

Before embedding the cells collected from the washings in paraffin, an erythrocyte lysis buffer (155 mM NH4Cl, 10 mM KHCO3, 1 mM EDTA, pH 7.4) was used to limit the amount of red blood cells which would impair visualisation during analyses. For each patient, two sets of formalin-fixed paraffin-embedded samples were obtained from the first and second washing. These samples were then cut at different levels and the tissue was stained with haematoxylin and eosin (HE stain). Next, the specimen slides were reviewed by an experienced pathologist (T.B.) to detect the presence of leiomyoma cells. In case of doubt, an additional staining with desmin was performed.

Data from the medical record of the patients were also abstracted and included: patient age and body mass index (BMI), indications for myomectomy, the number and weight of removed fibroids, and surgical outcomes such as operative time, intra-operative blood loss and complications. Complications were defined based on the classification of the Dutch Society of Obstetrics and Gynaecology.[7]

Results

Five patients were recruited to the study between April and October 2015. Patients were on average 34.6 years old (29– 40), with a BMI of 27.7 (22–34.1). Reasons for the surgery were heavy bleeding (n = 2) and/or infertility problems (n = 3) and/or pelvic pressure and pain (n = 2). On average, 3.8 fibroids (3–6) were removed and the removed specimens weighed 599.4 g (256–1040). All procedures were successfully completed, with an operative time of 108 min (91–134) and intra-operative blood loss of 685 ml (275–1300). Two patients experienced intraoperative haemorrhage of more than 1000 ml. One of them received two packages of red blood cells postoperatively. No other complications occurred and the postoperative course was otherwise uneventful in all cases (Table 1). All peritoneal washings obtained directly after opening the abdomen were negative, whereas three of the five peritoneal washings acquired after resection of the leiomyomas were positive for leiomyoma cells (Table 1, Figure 1). In one case the presence of leiomyoma cells was confirmed after performing an additional staining with desmin.

Table 1: Baseline characteristics, surgical outcomes and outcomes of cytology peritoneal washings

	Age (years)	BMI (kg/m^2)	Indication surgery	Operative time (min)	Intra-operative blood loss (mL)	Specimen weight (gram)	Number of fibroids (n)	Complications	First washing	Second washing
Patient 1	38	22.0	Infertility	100	275	256	3	--	Negative	Negative
Patient 2	31	27.8	Blood loss	103	1065	1040	3	>1000 mL blood loss + two RBCs	Negative	Positive*
Patient 3	29	26.1	Pressure + infertility	111	350	811	6	--	Negative	Positive
Patient 4	35	34.1	Blood loss + infertility	91	430	500	4	--	Negative	Positive
Patient 5	40	28.4	Pressure	134	1300	390	3	>1000 mL blood loss	Negative	Negative
Mean	**34.6**	**27.7**	--	**108**	**684**	**599.4**	**3.8**	--	--	--

*Desmin stain conclusive.

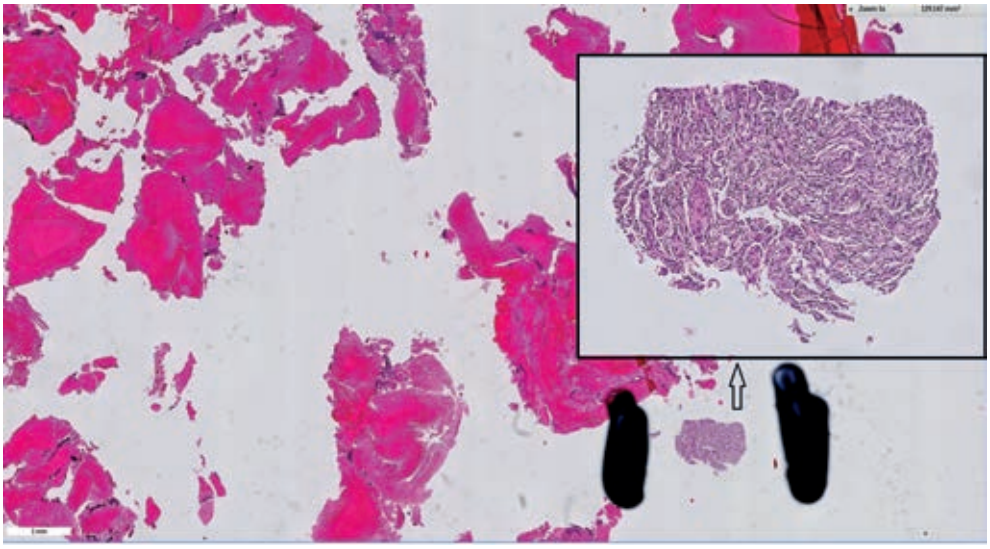

Figure 1: Leiomyoma cells (arrow) in the second peritoneal washing of patient 4 (HE stain).

Discussion

Main findings

There is evidence of micro-spillage of leiomyoma cells after conventional, open myomectomy but it is unclear whether these positive cytology results hold any clinical relevance if malignant change within the enucleated leiomyoma(s) is subsequently diagnosed following histological analysis.

Strengths and limitations

One limitation of our study could be the restriction of analysis to a conventional open abdominal myomectomy. However, the process of mechanically enucleating fibroids is similar during laparoscopic surgery and so one would expect the likelihood of tissue dissemination during myomectomy to be the same. The finding that tissue dissemination was not consistent following myomectomy, as no leiomyoma cells were detected in two of the five study cases, could be explained by the known limitations of the peritoneal washings technique[8] and so does not completely exclude their presence. In any case, even one positive cytology result would have been sufficient to support our hypothesis that dissemination of leiomyomatous tissue can occur during resection of leiomyomas. Our study analysed tumour dissemination of benign leiomyoma cells and not of leiomyosarcomas. Dissemination of leiomyosarcomas might also depend on whether small foci of sarcoma are at the edges of the excised specimen and/or breaches were made on the surface. Of note, in this study we focused only on myomectomy and so our conclusion can not be extrapolated to hysterectomy in the presence of uterine leiomyomas.

Interpretation

The present study sheds new light on the current morcellation debate. In reaction to the FDA report warning of the use of power morcellation in the presence of uterine leiomyomas, gynaecologists throughout the world have sought to develop techniques to reduce the risk of potential spread, while conserving the less invasive laparoscopic approach. In addition to reducing surgical morbidity, preservation of the laparoscopic route of surgery seems reasonable given the low prevalence of leiomyosarcoma compared with that of leiomyoma.[9]

One of the suggested surgical options is 'contained power morcellation': after resection of the uterus or fibroid, a bag is inserted into the abdomen and the specimen is morcellated in the bag and removed.[10,11] In many clinics, contained power morcellation has been rapidly adopted and the first studies have shown that, despite a prolonged operative time of approximately 20–30 minutes, the technique is feasible.[12-14] Even though this technique is in its early phase of development, it can be questioned whether containment after extensive resection without a bag will ever provide any additional safety during myomectomy, as our study showed that during leiomyoma resection, tissue dissemination already occurs. Furthermore, studies evaluating the leakage during contained tissue extraction with power morcellation noted spillage of tissue from the bag in 9.2–33% of cases.[15,16] However, in all those cases the containment bags were visually intact.

In light of this, it is important to evaluate the impact of intra-abdominal malignant tissue dissemination on patient outcomes. Several studies have suggested that spread of uterine sarcomas leads to an upstaging of the disease and dramatically worsens the five-year survival rate when compared with surgery where no morcellation was performed.[4-6] Although the assumption that malignant tissue dissemination is associated with poorer outcomes seems instinctively plausible, we should be careful with the concept of upstaging used in the studies. Indeed, it implies that during initial surgery all leiomyosarcomas were stage I and that staging was based on a proper inspection of the abdomen, which seems unlikely when a benign tumour is expected.[17] Other studies have found no differences in survival rates between the morcellated and non-morcellated group, or have stated a lack of reliable evidence regarding the clinically relevance of the spread, especially as generally speaking the overall prognosis of a leiomyosarcoma is poor.[17,18] Furthermore, it is unknown whether a relation exists between the amount of tissue dissemination and the recurrence and/or survival rate, especially as advanced research demonstrated already detectable circulating tumour cells in the blood of patients with early-stage localised tumours.[19]

The influence of non-radical procedures on the recurrence and survival rate has also been investigated in other malignant tumours. For endometrial carcinoma, similar

washing studies have been performed, showing an increased percentage of positive cytology after dissemination of tissue from the endometrial cavity into the peritoneal cavity[20] but with inconsistent results regarding the prognosis and recurrence of the disease.[8, 20] Also for ovarian carcinoma, controversy exists regarding the magnitude of harm of tumour leakage.[21] In a meta-analysis on early-stage ovarian cancer, pre-operative ruptures were associated with poorer outcomes compared with intra-operative ruptures,[22] probably due to the duration and the amount of leakage in the abdomen.[21-23]

From a benign perspective, a condition called parasitic leiomyomas has been reported and although the exact aetiology remains unclear, it is believed to be caused by retained intra-abdominal tissue fragments.[24] The overall risk of parasitic leiomyomas after uncontained morcellation has recently been reported as between 0.12 and 0.95%.[24] It would be interesting to know whether the prevalence changes with contained morcellation. Assuming that containment keeps macro-spread to a minimum during surgery, it cannot be excluded that micro-spread contributes to this rare condition. One recent published report recommended extensive washings after surgery to minimise the risk of retained tissue.[18]

Thus it is apparent that the impact of tissue dissemination on clinical outcomes is unclear, as is the protective value of contained extraction. Therefore, we believe that the gynaecological community should be cautious in widely adopting the peri-operative use of containment bags, which are most likely used off-label and without a proper systematic evaluation prior to implementation. Otherwise, there is a risk of offering a false sense of security. Furthermore, containment extraction should not distract us from seeking improved diagnosis of leiomyosarcomas and a better understanding of tumour biology including the impact of tissue dissemination on clinical outcomes.[25]

Conclusion

During open myomectomy, spillage of leiomyoma cells occurs. Although the clinical relevance of tissue dissemination after myomectomy is unclear, it cannot be excluded that it does negatively affect the patient's outcome, especially in the presence of malignancy. As a result, it can be questioned whether contained morcellation, as currently performed after laparoscopic myomectomy, guarantees any additional oncological safety.

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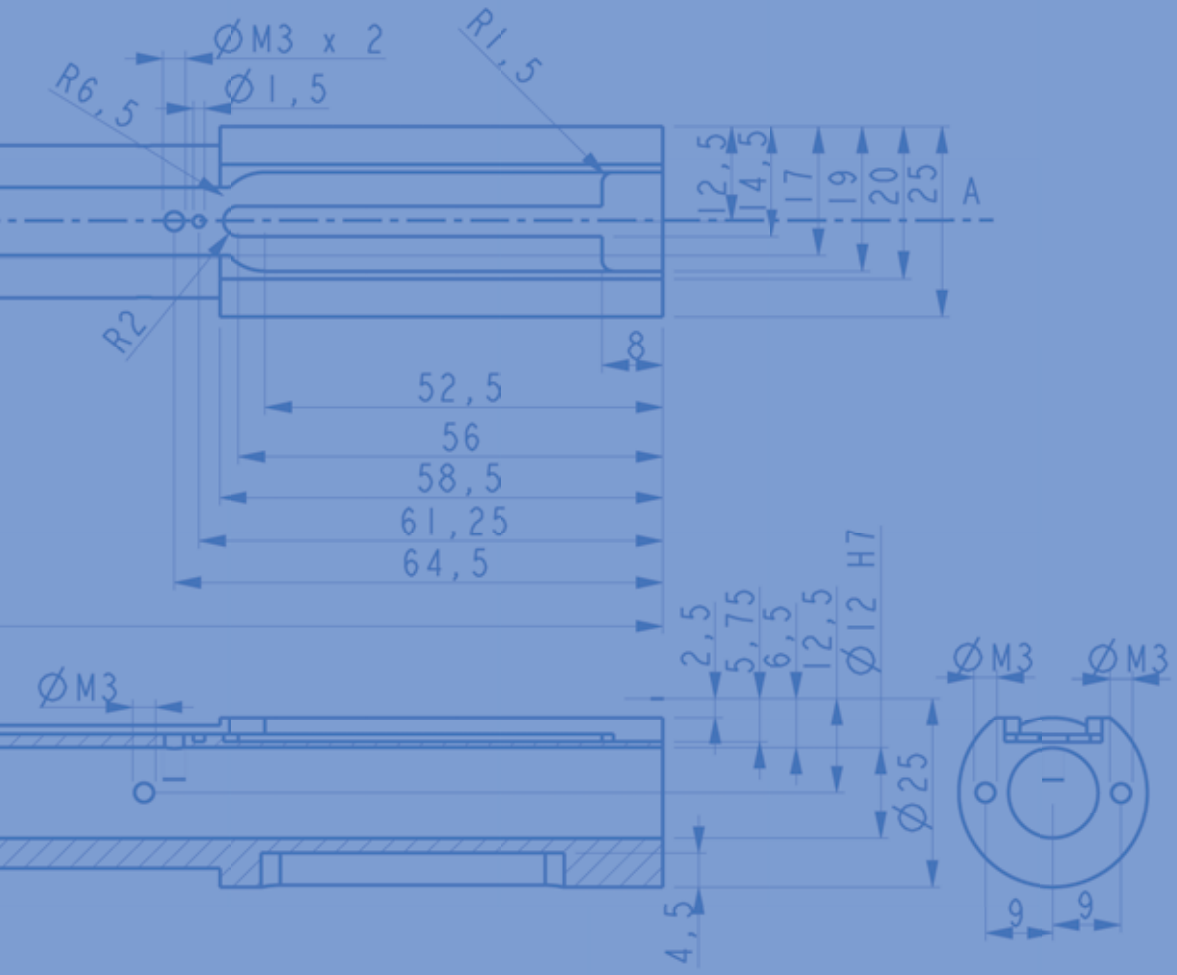
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Towards spill-free in-bag morcellation: a health failure mode and effects analysis

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Surg Endosc. 2018 Jul 9.

Abstract

Background: To assess potential risks of new surgical procedures and devices before their introduction into daily practice a prospective risk inventory (PRI) is a required step. This study assesses the applicability of the Health Failure Mode and Effects Analysis (HFMEA) as part of a PRI of new technology in minimally invasive gynecologic surgery.

Methods: A reference case was defined of a patient with presumed benign leiomyoma undergoing a laparoscopic hysterectomy or myomectomy including in-bag power morcellation; however pathology defined a stage I uterine leiomyosarcoma. Using in-bag morcellation as a template, a HFMEA was performed. All steps of the in-bag morcellation technique were identified. Next, the possible hazards of these steps were explored and possible measures to eliminate these hazards were discussed.

Results: Five main steps of the morcellation process were identified. For retrieval bags without openings to accommodate instruments inside the bag, 120 risks were identified. Of these risks, 67 should be eliminated. For containment bags with openings 131 risks were identified of which 68 should be eliminated. Of the 10 causes most at risk to cause spillage, two can be eliminated by using appropriate bag materials. Myomectomy appears to be more at risk for residual tissue spillage compared to total hysterectomy.

Conclusion: The HFMEA has provided important new insights regarding potential weaknesses of the in-bag morcellation technique, particularly with respect to hazardous steps in the morcellation process as well as requirements that bags should meet. As such, this study has shown HFMEA to be a valuable method that identifies and quantifies potential hazards of new technology.

Keywords: Hysterectomy; laparoscopy; morcellation; myomectomy; sarcoma

Introduction

A prospective risk inventory (PRI) assesses potential hazards of new surgical procedures and devices (henceforth called technology) before their introduction in daily practice. [1] However, prospectively assessing potential hazards of new and therefore unknown technology is challenging and methods are needed to aid this assessment.

The Failure Mode and Effects Analysis (FMEA) is a step-by-step method, performed by a group of people involved in the process, aiming to identify failure modes and their effects before new technology is introduced in daily practice. Failure modes are manners in which a process may fail, and the effects analysis examines the consequences of these failures. The HFMEA was developed in 1949 to prospectively evaluate problems that might occur due to malfunctioning of new military systems.[2]. Due to its prospective nature, the conclusions are based on inductive reasoning. Nowadays, an FMEA is an important tool in safety and reliability engineering of consumer products, such as the car industry. The FMEA was adapted to also suit healthcare requirements: the Health Failure Mode and Effects Analysis (HFMEA). However, experience with this method as part of a PRI is limited. [3,4]

The goal of our study was to assess the applicability of the HFMEA for new technology in gynecology. We used the efficacy of in-bag morcellation, with respect to the prevention of tissue spillage during morcellation, as a template for this method. Currently in minimally invasive gynecologic surgery (MIGS), in-bag morcellation is nearly regarded as the new gold standard for morcellation procedures to overcome the past safety issues regarding the spread of potential malignant tissue. The results of in vitro tests regarding the efficacy of containing tissue are favourable and the clinical feasibility has been demonstrated. [5-8] However, the oncological safety has yet to be proven. Furthermore, comparative trials are no longer ethically feasible, and prospective clinical data will only become available in several years. In theory, the HFMEA procedure overcomes these shortcomings of standard research methodology and provides necessary safety information of the in-bag morcellation technique in its early phase of implementation in daily clinical practice.

Materials and Methods

The HFMEA was performed according to the instructions of the prospective risk analysis system developed by the Department of Veterans Affairs, National Center for Patient Safety.[3]

The analysis consisted of 5 steps: choosing a subject, assembling a team for the analysis, describing the complete process of the subject of interest, performing a hazard analysis of the entire process and finally resolving all serious hazards.

Step 1: choosing the subject

To maintain a workable analysis of the subject of interest, it should be defined as precise as possible. This allows the number of actions and potential hazards to be limited to the ones that are most essential to the subject. For our study, a fictional case was defined of a patient with undiagnosed stage I uterine leiomyosarcoma, undergoing a laparoscopic hysterectomy (LH) or myomectomy (LM) including in-bag power morcellation for presumed benign leiomyoma. This scenario was chosen as in theory these patients are most likely harmed by the occurrence of spillage of malignant cells due to an immediate upstaging of the disease, resulting in a significantly worse prognosis. Our focus being on spillage, risks considered inherent to all (laparoscopic) surgical procedures were excluded from the scope of the present study.

Step 2: assembling the team

A team is assembled representing most of the health care workers who are involved with the subject of interesting. An expert in the subject and a team leader are appointed. The expert helps explaining the process, and the team leader chairs the meetings. Novices to the process are also part of the team to promote an unbiased critical view of current practice.

Step 3: describing the in-bag morcellation process

Next, the studied subject is graphically described in a flow diagram. The main steps are defined and then for each main step the sub-steps are identified. Two types of morcellation bags were assessed: regular specimen retrieval bags without openings to accommodate instruments thus consequently in need of iatrogenic breach of bag integrity, and containment bags equipped with openings to accommodate a camera or instrument. Furthermore, morcellation after LH and after LM was evaluated.

Step 4: hazard analysis

For the complete process as determined in step 3, all possible hazards (so called failure modes, meaning how and why a process might fail) are identified. To rank these hazards from most to least serious, these failure modes are scored for their impact on patient health or safety ('severity') and their chance of occurring ('probability'). By multiplying the scores for severity and probability, a hazard score is calculated: high scores correspond with serious hazards. Severity was classified according to the following 4 categories: recovery without intervention (1 point), intervention needed for recovery (2 points), permanent damage or loss of function (3 points), death (4 points).(9) (Table 1).

Table 1: Probability and severity score. Red: hazard score ≥ 8 represents a safety issue and should be addressed.

Probability	Severity				
		Death	**Permanent damage**	**Recovery with Reintervention**	**Spontaneous Recovery**
	> 1/10	16	12	8	4
	1/10 – 1/100	12	9	6	3
	1/100 – 1/1000	8	6	4	2
	< 1/1000	4	3	2	1

To maximize results of our analysis, any kind or amount of tissue spread or leakage was considered potentially lethal. 'Probability' was defined as occurring: in less than 1000 procedures (1 point), between 1 in 100 and 1000 procedures (2 points), between 1 in 10 and 100 procedures (3 points), 1 in 10 or more (4 points). A mean hazard score was calculated based on the individual scores provided by all participants. All participants calculated the hazard scores individually. Next, the scores were compared during the meetings and, in case of disagreement, discussed and adjusted to reach full agreement upon the final hazard score.

Step 5: resolving serious hazards

The HFMEA decision tree is used to identify the failure modes that may cause safety issues and should therefore be eliminated. [3] In short this decision tree identifies all hazards with a hazard score ≥ 8 as a potential threat that needs to be addressed (colour *red* in table 1). Readily apparent hazards and hazards that are already known and controlled can be exempted. In addition, the decision tree identifies all critical steps in the process (so-called single point of weaknesses, meaning that the technique would fail if this single step fails) even with a hazard score <8.

After identifying these hazards, recommendations were formulated in our final meeting to eliminate the most hazardous steps of the in-bag morcellation procedure .

Results

A total of 7 participants were selected for the HFMEA: 1 gynecologist-oncologist, 1 gynecologist specialised in MIGS, 1 urologist specialised in minimally invasive surgery, 1 operating room (OR) nurse, 2 residents in gynecology and 1 researcher in MIGS.

The senior author acted as the expert on the in-bag morcellation process. An expert in surgical instrument safety with experience in HFMEA procedures (ACE) was appointed as team leader. To complete the five steps, six sessions of 2 h (in total 12 hours) were needed, followed by additional discussion via email. During the first two sessions, five main steps of the morcellation process were identified. The first step is inserting the bag in the abdomen. This involves unwrapping the bag, handing it to the OR nurse and then to the surgeon, until the bag is correctly placed inside the abdomen. In step 2, the tissue is placed in the bag, meaning that the tissue is grabbed by surgical graspers and is manipulated inside the bag. In step 3, the bag is positioned for morcellation and inflated with CO_2 gas. For specimen retrieval bags without extra openings, this also involves the iatrogenic puncture of the bag to accommodate surgical instruments and inflation of the bag. In step 4, the tissue is morcellated and extracted until all tissue has been removed. Finally in step 5, the bag is retrieved from the abdomen and the abdomen is inspected for tissue residue. Figure 1 demonstrates these steps, as well as the number of sub-steps that were found for each main step. As an example, the sub-steps of main step number 4 (morcellation and extraction of tissue) are described in full in the same diagram.

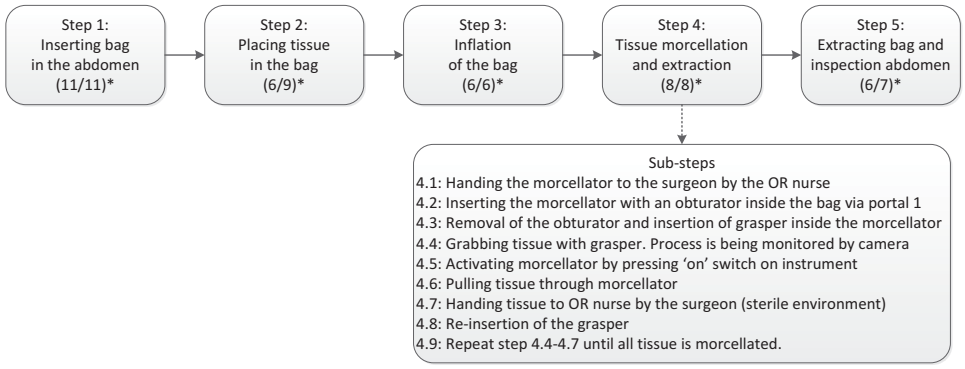

Figure 1: All main steps of the morcellation process. *number of sub-steps for each main step: (retrieval bag without sleeves / containment bag with sleeves). Arrow (bottom): sub-steps of main step 4 'tissue morcellation and extraction'.

For regular retrieval bags without openings, 37 sub-steps and 120 failure modes were identified. Of these failure modes, 67 could be eliminated. For containment bags with openings, 41 sub-steps and 131 failure modes were identified. Of these, 68 were identified as possible hazards that could be eliminated.

In Table 2, for both bags the moments of the in-bag morcellation procedure most at risk for tissue spillage (meaning with the highest hazard scores of 16) are supplied. These moments consist mainly of steps where tissue fragments may spread throughout

Table 2: top hazard scores for both type of bags.

Failure mode	Cause	Possible prevention
Contamination of the outside of bag	**Grasping with contaminated instruments** **Contact with exposed myoma**	**Inherent to myomectomy procedure**
Contamination of surgical instruments before morcellation	**Grasping myoma**	
Contamination of the abdominal cavity, peritoneum or abdominal wall	**Contact with the outside of the bag that was contaminated during main steps 1 and 2**	
	Spreading of remnant tissue by airflow of the pneumoperitoneum	Remove all tissue from abdomen / place all tissue in bag
Contamination of the camera and surgical instruments situated inside the bag	By tissue fragments being spread during morcellation	Clean camera and instruments before re-insertion into abdominal cavity after morcellation procedure
Contamination of surroundings and instrument table	By handling of the contaminated morcellator, contaminated camera or instruments	Prevent contact as much as possible, use a different instrument table and consider changing gloves in case of full contact
Occurrence of tissue spillage	Bag or tissue damage due to sharp graspers and other sharp instruments	Use appropriate non-sharp instruments
Contamination of trocars	*By contact with tissue inside bag when trocar is used to perforate bag*	*Avoid using regular bags without a pre-fabricated insert for camera*
Contamination of the abdominal cavity, peritoneum or abdominall wall	*By leakage of tissue through perforation during extraction of the bag from the abdomen*	

Bold: hazards specific for myomectomy. *Italic:* additional specific hazards for regular bags in need of perforation before morcellation.

the abdomen by instruments that have come in contact with the morcellated tissue. Possible measures to control these risks are also proposed in table 2. Hazards specific for myomectomy and additional hazards of retrieval bags without openings are highlighted in the same table. Four out of 10 causes most at risk to cause spillage, are specific for myomectomy and do not occur during hysterectomy. Two more causes can be eliminated by avoiding the iatrogenic puncture of retrieval bags without openings to accommodate the camera or morcellation instrument.

Discussion

Using in-bag morcellation as a template, our study assessed the applicability of the HFMEA method as part of a PRI for new technology. Although the in-bag morcellation technique is already widely used in daily clinical practice, the HFMEA revealed several possible weaknesses that should be addressed to further enhance the safety of this procedure.

All instruments (camera, graspers, portals) used inside the bag are a possible source for tissue spillage. In theory, when these instruments are later re-introduced into the abdominal cavity they may unintentionally insert tissue remnants that were initially contained in the bag. Also, handling these instruments and placing them on the instrument table may contaminate the surgical team itself and other instruments. However, in case of sarcoma the oncological effect of minimal amounts of spread or leakage, henceforth called micro-spillage, into the abdominal cavity is unclear. For instance, in endometrial carcinoma the spread of malignant cells in the abdominal cavity via the fallopian tubes during hysteroscopy, does not appear to negatively influence clinical outcome.[10-12] The same might apply to our findings. Nonetheless, in theory it seems appropriate to thoroughly clean or even change all instruments and surgical gloves after morcellation. In the same light, it became clear that myomectomy is at higher risk regarding tissue spread compared to hysterectomy. Tissue spillage during myomectomy has been demonstrated even without morcellation.[13,14]. Therefore in myomectomy, tissue may have spread both during and after the excision of the myoma, even before morcellation is performed. This does not occur after (total) hysterectomy, assuming that the integrity of the leiomyosarcomas is preserved. It follows that four out of 10 causes most at risk for spillage, can be eliminated when comparing hysterectomy to myomectomy.(table 2) It should be stressed however, that the meaning of micro-spillage is unclear and this study does not propose to abandon the minimally invasive removal of fibroids. Yet in this light, the possible consequences of micro-spillage should be further studied to reach a complete understanding of the risks of morcellation.

The second main hazard for contamination is failure of bag integrity due to sharp instruments handled in or around the bag. Yet, this can be easily eliminated. Only materials should be used that can withstand forces applied during power morcellation, including instrument and tissue manipulation, as well as pressure and airflow caused by insufflation of the bag. In addition, bags should remain impermeable to tissue cells under these conditions. Furthermore, gynecologists should be aware of bag integrity failures when using their instruments near the bag.[5,15] Finally, the design of containment bags should be able to accommodate the camera, morcellator and possibly a third instrument in the bag. The intentional puncture of retrieval bags has already been shown as possible cause for tissue leakage during in-bag morcellation.[7] By avoiding this puncture, 2 of the 10 (LM) and 2 of 6 (LH) main causes for spillage can be eliminated. (Table 2) To our knowledge, of the currently available morcellation bags only one claims to meet the above mentioned requirements. This bag was recently permitted to market by the FDA.[16]

There are some considerations when interpreting the results from our study. Firstly, the consequence of micro-spillage is unclear as discussed. Nevertheless, there is increasing evidence that disease outcome is negatively influenced after (all types of) morcellation.[17-20] Next, there are limitations regarding the HFMEA.

This method was considered too time consuming in some studies and concerns were raised regarding the external validity of the prioritizing of hazards in the HFMEA.[21,22]. The severity and probability of a potential hazard may not always be known and must therefore be estimated by the team. In addition, hazards may be overlooked altogether. On the other hand, the identification of all (sub)steps and hazards of a procedure was reliable and reproducible.[22] In our opinion, this is the most important component of the HFMEA as the identification of such hazards, regardless of prioritization, allows adjustments and improvements of the assessed technology. Finally, although the HFMEA was time consuming, the time we spent is insignificant in relation to the time needed to repair adverse events that could have been prevented with a thorough prospective evaluation. Indeed it can be questioned if a thorough risk analysis of power morcellation would have resulted in early warnings regarding the spill of malignant tissue being taken more seriously.[23-27]

In conclusion, this study has demonstrated that the HFMEA is a valuable part of a prospective risk inventory of new surgical technology. Using in-bag morcellation as a template, the HFMEA has provided important new insights regarding potential weaknesses of this technique that were previously not recognized, even though in-bag morcellation is proposed as the new standard for morcellation. In addition, the recommendations that resulted from the HFMEA could be easily implemented in daily clinical practice.

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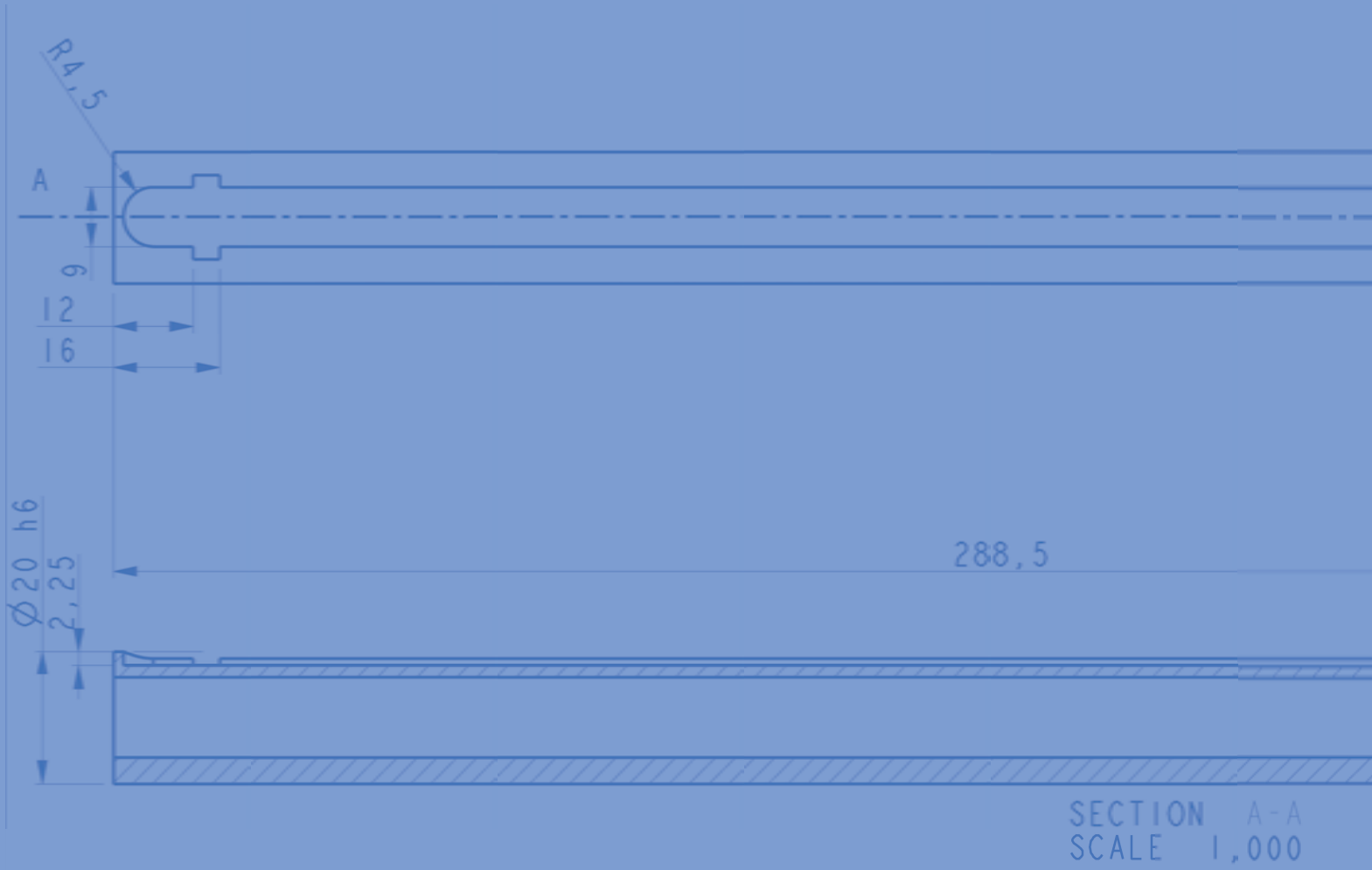
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Discussion and Future Perspectives

11

Discussion

Approximately 500.000 types of medical instruments are used in daily clinical practice, ranging from blood pressure meters to advanced surgical robots.[1] Although regulating bodies exist that oversee the introduction of new instruments, a grey area exists whether a new technology is merely an improvement of an already existing and approved instrument or implies such significant changes that would justify generating a new safety protocol. Furthermore, the prudence with which new technology is introduced may often depend on the sense of responsibility of the medical specialist.[2] A growing awareness exists, however, that new instruments inherently have the potential to negatively influence patient safety due to unforeseen side effects. In the past serious short- and long-term adverse events have been described, some of which are discussed in the introduction.[3-7] Several reports were published proposing alternatives to better safeguard patient safety during the implementation of new medical devices.[1,2,5,6] In general, emphasis is placed on proper studies performed in human subjects. As such, randomised controlled trials are considered as highest level of evidence to demonstrate the superiority of an innovation compared to standard techniques. However, we hypothesized that much can be gained regarding patient safety by enhancing the pre-clinical course during the development of a new instrument. In the *leidraad nieuwe interventies in de klinische praktijk* the importance of this course is acknowledged.[2]

In this thesis we focussed on the earliest phase of the development of new surgical instruments, also known as stage 0. It assessed various pre-clinical evaluation methods for new instruments.

Clinically driven approach

Firstly, the concept of a *clinically driven approach* to the development of a new surgical instrument was explored. In general, three approaches exist when trying to enhance daily medical practice. When new technology is devised by the medical industry or by engineers, the approach is called *commercially driven* or *technically driven* respectively.[8,9] Although these approaches can lead to medical devices that are state-of-the-art technically speaking, they may not always meet the demands of clinicians possibly rendering them useless.[9] The *clinically driven approach* starts with identifying a medical or surgical difficulty experienced by the users (i.e. physicians), which is then used as a starting point to create a solution. Usually this implies a close cooperation with technicians and or the medical industry.[10,11]

In our research, the laparoscopic hysterectomy (LH) was chosen as the starting point for exploring the clinically driven approach. The LH is a frequently performed gynaecological

procedure worldwide, but is also considered as technically challenging. Two major topics were addressed.

In **Chapter 2**, we demonstrated that the colpotomy step during LH (meaning the separation of the vagina from the cervix, generally the penultimate step of LH before suturing the vaginal vault) is regarded by gynecologists as difficult and time-consuming. This was substantiated by the measurements of total operation time and colpotomy time. Furthermore, we found that BMI was positively related to colpotomy time, independent from total operation time. As BMI in the general population is rising, colpotomy may increasingly be the limiting step during LH.[12] Subsequently, in cooperation with technicians from the University of Technology in Delft, The Netherlands, an alternative to the current colpotomy procedure was searched. It was proposed that a vaginal approach to colpotomy could possibly overcome present issues with this step in the LH procedure. This resulted in a prototype, called MobiSep, which combines the function of a uterine manipulator and a cutting function to seperate the vagina from the cervix.[13]

A uterine manipulator is an important instrument used during laparoscopic procedures in gynecology as it allows movement and steering of the uterus during surgery. It is proposed that the use of a uterine manipulator should be mandatory because it is said to prevent against ureteric injuries during LH by displacing the ureters from the uterine arteries.[14] In **chapter 3** a literature review was performed as a method to explore the required characteristics that the envisaged prototype should meet. The shortcomings of existing manipulators were used to improve the prototype. It was found that few manipulators offer lateral movement of the uterus, whereas at the same time this movement is regarded as important during ligation of the uterine arteries. Surprisingly, little evidence was found regarding the efficacy of uterine manipulators. For instance, only one observation existed in literature that reported an increase in distance between the ureter and uterine artery due to a uterine manipulator, however methods and materials were not supplied.[15] It is worrying that in the same article it was also observed that the distance can actually decrease due to a mismatch between the size of the cervical cup of the manipulator and the cervix. This would imply that in some cases, there is even more risk of ureteric injuries. Based on the results from our literature review, a study was performed evaluating the relationship between the ureter and uterine artery with and without a manipulator. In one case an increase was observed between the two structures.[16] However, this could not be replicated in the second case. [oral, Lieng] In conclusion, important insights were gained, not only regarding the characteristics of the prototype, but also regarding the workings of uterine manipulators in general.

The next step in our *clinically driven approach* was to assess the prototypes performance and to evaluate if changes should be made before the instrument is ready for a clinical

trial. However, an ideal model in which the new prototype had to be tested could not be found. Animal models are generally not representative due to different anatomy of the internal genitalia. In addition, currently available virtual reality tools bear little resemblance to real life conditions such as tactile feedback. For training purposes, human cadavers have been shown to be a valuable method to improve surgical skills. [17-19] Furthermore, human cadavers were preferred over virtual reality simulators. [20] Based on these findings, in **chapter 4** we decided to assess human cadavers as a model for testing new surgical instruments. Fresh frozen cadavers were chosen as they were favoured in training purposes with respect to tissue appearance and handling. [19,21] The results from the cadaver tests demanded that extensive modifications were applied to the prototype. Although the MobiSep was extensively tested in an in-vitro model, serious anatomical shortcomings of the design were encountered that were not revealed by the in-vitro model. As such, the cadaver tests added essential information to the developmental phase of MobiSep. However, significant limitations were encountered of cadavers as models. Only two of six human cadavers resembled normal anatomy of the internal genitalia. Other cadavers could not be used due to restrictions caused by age-induced atrophy, congenital abnormalities and a malignancy occupying the complete small pelvis. Unfortunately, the medical history of a cadaver is not disclosed due to privacy legislation. Given the low efficiency, it is questionable if human cadavers should be used on a larger scale during the pre-clinical assessment of new technology. In this light, the ongoing developments in 3D printing are of interest. Recent papers have studied the value of 3D printed models for training purposes, and the feasibility of creating representative models of human anatomy has been demonstrated.[22-24]. Several applications already exist in clinical practice. For instance in orthopaedic surgery, 3D printing is already used to preoperatively adept surgical plates and screws to a patient's anatomy.[25] However, currently the main shortcoming of 3D printed models is the lack of resemblance to the natural compliance of human tissue.[26] When this issue is resolved 3D printing will ensure a major improvement of stage 0 of surgical innovation.

The second topic that we addressed concerns power morcellation in laparoscopic hysterectomy and myomectomy. It was observed that during morcellation, small tissue particles are dispersed throughout the abdomen (called tissue spill or spillage). In case of uterine malignancies, it is believed that this tissue spill causes upstaging of the disease and can therefore negatively affect a patient's prognosis.[27,28]

We attempted to address this issue by improving the power morcellation instrument. To this end, we first examined the onset and characteristics of tissue spillage during morcellation in **chapter 5**. Next, in **chapter 6** instrument characteristics that could influence the onset of tissue spillage were assessed. Important inefficiencies were demonstrated of the power morcellator mechanism available at that time. The onset of

torque (also called moment of force) was found to be the cause of tissue spillage. Torque is a rotational force applied to an object. Ideally the rotational blade of a morcellator only slices tissue without applying force to the tissue. However, due to torque, the sliced tissue starts to rotate uncontrollably resulting in tissue particles being dispersed through the abdomen. It was observed that only at the very beginning of the morcellation procedure large tissue segments were created by the instrument. During the majority of the procedure (60%) only small particles were created. These smaller fragments are easily subjected to torque. Also, the amount of tissue spillage was not linearly related to uterine weight, suggesting that after a certain point the risk of tissue spill increases significantly. Finally, it was found that larger diameters of the morcellation instruments (up to 20mm) and an oscillating blade rather than a rotational mechanism all decreased the amount of spill. These findings offered valuable information regarding the shortcomings of the current morcellators that were previously unidentified. Although the devices have been improved through time regarding speed of morcellation, no initiatives were taken to assess other parameters.[29] For our study, beef tongue was used as a model for the human uterus. This cheap and easily obtainable material matches the consistency of the uterus well and was successfully used in other studies.[30-32] Also in our assessments, beef tongue resembled uterine tissue very well. Thus, for simple and straightforward testing of instrument characteristics expensive models are not necessary.

Interestingly, the finding that larger instruments create less tissue spill and may therefore be safer appears to be in contrast to the ongoing developments in minimally invasive surgical techniques. More and more, the invasiveness of surgical procedures is reduced as much as possible as is shown by developments in laparoendoscopic single-site surgery (LESS) and natural orifice transluminal endoscopic surgery (NOTES). However, the benefits of these procedures are not always clear and possible risks have been described. [33] Apparently, smaller is not always better. After identifying torque as the main cause of tissue spillage, it was quickly understood that morcellation instruments with a smaller diameter cause more spill since torque is applied earlier the process.

The findings from chapter 5 and 6 were used to enhance the current morcellation mechanism. In **chapter 7** a prototype is discussed that resolves the problem regarding torque. Inspired by the lamprey, a fish resembling eels that use their teeth and suction to attach themselves to other fish and feed of their blood, an instrument was developed with similar teeth that fixate the morcellated tissue as it is inserted in the teeth-lined instrument. As such, it prevents the uncontrollable rotation of tissue fragments due to torque, thereby reducing tissue spillage.

Prospective Risk Inventory

In 2014, the *Leidraad Nieuwe Interventies in de Klinische Praktijk* was published by the *Orde van Medisch Specialisten* and the *Zorginstituut Nederland* with the support of the *Kennisinstituut van Medisch Specialisten*. [2] It aimed to structure the introduction of new technology into daily clinical practice to warrant safety, efficacy and cost-effectiveness, without raising thresholds for innovation.

A roadmap was created that emphasizes a careful consideration before the new technology is introduced. An important component of this roadmap is the prospective risk inventory (PRI). A PRI is an important item of a safety management system and intends to foresee risks in health care processes rather than to remedy adverse events after they have occurred.[34,35] No fixed model for a PRI is provided, since possible risks depend on specific situations and thus may vary per hospital. The range of the PRI procedure is defined by the associated risk of the technology and the frequency of its use.[2] (Figure 1) Low risk medical devices that are used on a large scale may still imply that a significant amount of patients may suffer from associated adverse effects. For instance, glucose meters appear to be low risk and easy to use. However, should these instruments malfunction or be misinterpreted the consequences may be detrimental if this leads to an overdose of insulin. The chance of this occurring may be small, however these instruments are widely used by diabetes patients and medical personnel. In contrast, high-risk medical devices that are used sporadically may not cause harm on a large scale, yet may cause severe damage to the individual. Power morcellators are an example of such high-risk devices. Both scenarios require an extensive PRI according to figure 1.

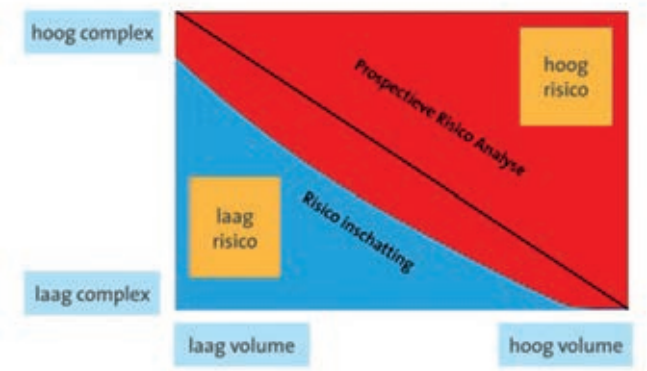

Figure 1: Relationship between risk and volume of a new technology and the range of a prospective risk inventory. (From: Leidraad Nieuwe Interventies in de Klinische Praktijk)

In this thesis, the concept of the PRI is applied to the morcellation issue as previously discussed. The high risk of encountering an unexpected uterine sarcoma led to the decision of the FDA discouraging the further use of power morcellators. It was previously calculated by the FDA that uterine sarcoma (US) and leiomyosarcoma (ULMS) may be present in 1 in 350 and 1 in 458 women undergoing hysterectomy or myomectomy for presumed benign fibroids respectively.[4] However this number has been criticized. It was calculated based on a limited number of studies which all consisted of data coming from referral centres.[36] Furthermore, high-risk patients were included (such as postmenopausal women and women with known malignancies) and varying definitions of sarcoma were used.[36] Recently the FDA has updated this risk of occult ULMS to 1 in 495 to 1 in 1100 women undergoing surgery, using data from more recent studies.[37] However, the initial FDA statement resulted in a worldwide decrease in the use of morcellators and in an increase in the number of laparotomies.[38-41] These outcomes appear to be in contrast to the advantages of MIS over laparotomy, which have been well established.[42] In fact, studies show morbidity and mortality in favour of MIS in most cases, even when including the accidental morcellation of uterine sarcoma.[43-46] However, the outcome in these prediction models strongly depend on the incidence of ULMS, making them difficult to use as long as this incidence is not better defined.

In **chapter 8**, we established the above mentioned risk of encountering unexpected ULMS during surgical procedures for presumed benign pathology. A nationwide cohort study was performed evaluating all ULMS diagnosed in The Netherlands between January 2000 and September 2015 using the database from the nationwide network and registry of histo- and cytopathology in The Netherlands (PALGA).[47] By using a nationwide database including secondary and tertiary health care centres the previous mentioned shortcomings of the number estimated by the FDA were eliminated. The risk of ULMS in women undergoing surgery was 1:385 or 0.26% for the whole group, and 1:795 or 0.13% for unexpected ULMS. Moreover, the risk for receiving non-standard treatment for ULMS (meaning abdominal hysterectomy with or without bilateral oophorectomy) in the unexpected group was even lower at 0.03% or 1:3333 patients. Using our results in the mentioned prediction models, it is shown that overall morbidity and mortality are in favour of laparoscopic procedures with morcellation as opposed to laparotomy procedures.[46] In addition, our study demonstrated that women aged 40-50 years of age presenting with abnormal uterine bleeding (AUB) are most at risk for unexpected ULMS. Unfortunately, this age group belongs to the age range with the highest ULMS incidence. Therefore in these women, the surgical approach to the removal of uterus or fibroids should be carefully considered. Reassuringly, in almost all postmenopausal women a ULMS was expected and consequently these women were at a low risk to undergo non-standard surgical treatment for ULMS. Finally, ULMS were very rare under

the age of 40 (only 4% of all ULMS cases). Therefore, minimally invasive or uterine sparing treatments could still be considered in these women.

To preserve the minimally invasive approach for the removal of uterus or fibroids, gynecologists are seeking to enhance the safety of power morcellation. In-bag morcellation is proposed as the *main* solution to the current safety issues and this technique appears to be promising. The results of in vitro tests regarding the efficacy of containing tissue are favourable and the clinical feasibility has been demonstrated.[30,48-50] However, long-term results are lacking and the oncological safety has yet to be proven. [51-54] In this light, results from in-bag morcellation techniques from other specialties should be considered. In urology it has been demonstrated that for low stage and low grade renal cell carcinoma laparoscopic nephrectomy with in-bag morcellation of the renal specimen appears to be a safe alternative to open radical nephrectomy. [55,56] However, there is evidence suggesting that this is not true for high stage/grade tumors (often displaying sarcoma-like characteristics).[57, 58] Given the aggressive nature of ULMS, in-bag morcellation should therefore be implemented with caution. Notwithstanding these limitations however, in-bag morcellation is currently nearly regarded as the gold standard for morcellation. As such, there is a risk that serious adverse events are overlooked and may reveal themselves in the future. In **Chapter 9** the rationale behind in-bag morcellation for myomectomy specimens was examined. It was hypothesized that tissue spillage occurs regardless of in-bag techniques. Leiomyosarcoma are heterogeneous tumours and malignant cells may be located anywhere in the leiyomyosarcoma, including at the cleavage plane used for myomectomy. Indeed, we demonstrated that myoma cells are spilled into the abdomen even before morcellation is performed. This observation has been substantiated in another study.[59] Therefore it can be concluded, that in-bag morcellation after myomectomy does not fully guarantee safety in case of unknown ULMS.

The PRI of in-bag morcellation was finalized in **chapter 10.** A Health Failure Mode and Effects analysis (HFMEA) was performed to prospectively identify moments in the morcellation procedure that are at risk for tissue spill.[60] The main finding was that although the spillage of larger particles can be avoided, the risk of spillage of small particles or microscopically amounts of spill remains due to contamination by instruments that came into contact with the morcellated tissue. Unfortunately, the clinical consequences of macro- versus micro-spillage are still unknown. For instance, in endometrial carcinoma the spread of malignant cells in the abdominal cavity via the fallopian tubes during hysteroscopy or dilation and curettage, does not appear to negatively influence the oncological outcome.[61-63] Yet, the negative impact of the morcellation of uterine sarcoma on the oncological outcome have been described, although not undisputable. [64] For instance, in one study characterized by a longer than average follow up, the

same recurrence rate was found in women with sarcoma confined to the uterus as in other studies with morcellated specimens.[65]

It should be questioned if our PRI would have revealed the adverse events of tissue spillage in its implemental phase in 1991. An important shortcoming exists of qualitative prospective methods such as the HFMEA. Insufficient knowledge of a procedure and the associated risks can lead to hazards not being identified or being over- or underestimated .[66,67] Recently, the FDA admitted its awareness of the possible spread of cancerous tissue when it approved the morcellation device.[68] However it was estimated that the chance of this occurring amounted between 1:1000 and 1:10.000 cases. Consequently this was not considered a significant risk. Already in 1997, only 2 years after the FDA approval of power morcellators, a report was published warning against the morcellation of undiagnosed malignancies.[69] In the following decade, similar studies were published on the topic, but up until 2014 these warnings were not acknowledged. Unfortunately, several developments were not considered in the initial risk estimation. For instance, uterus-sparing modalities are increasingly applied for the treatments of fibroids and abnormal uterine bleeding. One explanation for the surprisingly high incidence of ULMS in surgical specimens is, that as a result of this development nowadays only cases that are resistent to conservative treatment are treated surgically.[70] Furthermore, power morcellators have allowed the minimally invasive removal of increasingly large uteri, which previously would have been removed in total via laparotomy, thus the indications for a minimally invasive approach have extended.

Because of the limitations regarding risk estimations, it is suggested that an HFMEA is unsuited to study patient safety interventions.[67] However, the same study also demonstrated that the identification of hazards was valid and reproducible.[67] To overcome this flaw of underestimation of important hazards, the HFMEA method regards apparently small but possibly severe hazards as a “single point of weakness” that must be addressed before new technology can be implemented.[60] Another important critique is that the HFMEA is too time consuming and too demanding for hospital resources. Indeed, we spent over 12 hours discussing the in-bag morcellation procedure with 7 persons coming from 3 different departments of our hospital. In addition, time was spent to finalize the procedure via email. However, in our opinion the time that has been spent and is still spent on the morcellation subject since the FDA statement in 2014 quickly refutes this argument. Moreover, when patient safety is involved it should be questioned if too much time can be spent.

In all, it can be concluded that a timely PRI would perhaps not have resulted in a general warning regarding the spreading of cancerous cells, however it would have allowed a general awareness regarding this risk. With a more careful post-market surveillance,

early signs of adverse events may possibly have been taken seriously sooner. In addition, better insight in the actual incidence of ULMS would have alerted gynecologists to take caution when performing minimally invasive procedures in high-risk patients. Finally and most importantly, it would have allowed informed consent of the patient in the pre-operative workup. In a recent study it was demonstrated that patients were not averted from minimally invasive surgery when provided with information regarding the risks of morcellation during laparoscopic hysterectomy.[71]

Conclusion

The *clinically driven approach* to the development of new surgical instruments allows a close collaboration between clinicians and engineers. Several methods can be used to enhance a prototype before it is used on live humans for the first time. Surveys and literature reviews regarding instruments that resemble the proposed prototype are simple but effective tools to identify areas for improvement and gain insight in possible risks. Cheap and easily acquired materials such as beef tongue are valid models to assess favourable characteristics of new instruments. However proper models, including animal models, that resemble real-life circumstances are lacking in gynecology. Unfortunately, shortcomings regarding anatomical variations, the effects of freezing and thawing on tissue properties or the presence of pathology prevent human cadavers from becoming the gold standard model in stage 0 pre-human trials.

The prospective risk inventory offers a better understanding of a new procedure or surgical instrument and can therefore provide information regarding possible hazards. Performing an elaborate PRI is time consuming however. Since no strict guidelines exist regarding the extent and contents of the PRI and which procedures and instruments should be assessed, there may still remain a grey area where new instruments can escape a PRI before their implementation in daily clinical practice. Hospital-wide collaboration with respect to these aspects can eliminate this grey area and may reduce time by delegating tasks among this collaboration. To promote the sense of shared responsibility by hospitals, the implementation process could be organised into a so called “think-tank” where representatives of all hospitals participate. Recommendations derived from such a collaboration, can be swiftly applied in all hospitals without extensive additional scrutiny.

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Future Perspectives

It is clear that still much can be gained regarding patient safety during the development and implementation of new surgical instruments. The *clinically driven approach* as evaluated in this thesis resulted in a close collaboration between clinicians and engineers. This allowed quick feedback and input with respect to necessary modifications to the tested surgical instrument prototypes. Still, a large gap was discovered between the workings of new instruments in in-vitro models and their efficacy in human-like conditions. To close this gap, future research should focus on the development of easily accessible and life-like models. As such, 3D printed models are promising. However several shortcomings need to be addressed before they can successfully act as human-like models, mainly improving the resemblance to the natural compliance of human tissue. Enhancements in synthetics and biomaterials are therefore needed. Furthermore, virtual reality tools and computerized models can be valuable additions to *hands-on* testing of instruments, once these techniques are further improved to realistically reflect *real life* situations.

Regarding the power morcellator controversy, further research should be performed regarding the oncological effects of the spillage of microscopically small tissue fragments. Mouse models could provide a suited model to test the ability of a ULMS to metastasize via these spilled particles. The results of such research will finish the PRI of (in-bag) morcellation.

Several initiatives to further facilitate the *clinically driven approach* have already been installed. For instance, the University of Technology in Delft, The Netherlands has commenced a Bachelor of Clinical Technology, which aims to equip students with medical and technical knowledge, so they can form a link between technology and patients. Furthermore, a medical delta exists in the province of Zuid-Holland and the Twente region in which universities and colleges collaborate in health care innovations.

The next step in this collaboration would be the creation of centralized one-stop shops in hospitals where new innovations can be presented to a dedicated team who are educated to assess the safe implementation of the innovation in daily practice. These one-stop-shops should facilitate clinicians to present their innovations to engineers, thus providing an impetus to enhancing medical technology.

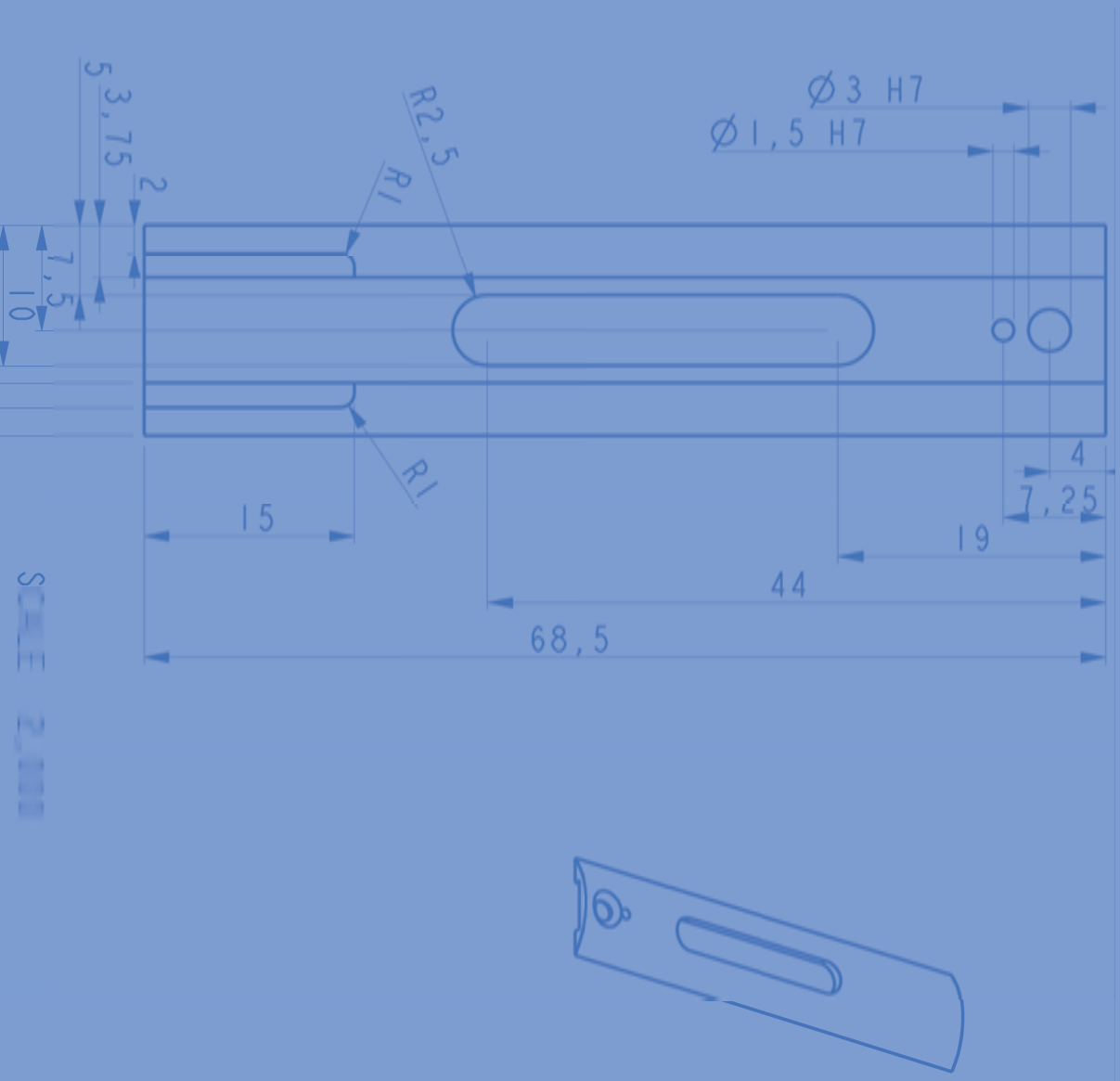
A *prospective risk inventory* should be an important item of this assessment, as its value was successfully demonstrated in this thesis. However, important questions need to be addressed. It is yet unclear if all innovations should undergo an elaborate PRI. Furthermore it is unclear who is responsible for the performance of a PRI: the manufacturer, engineer or physician. Since resources are limited, these are valid questions. It should

be attempted to coordinate a PRI as much as possible, to prevent several institutes performing the same procedure. To promote the sense of shared responsibility by hospitals, the implementation process could be organised into a so called “think-tank” where representatives of all hospitals participate. Recommendations derived from such a collaboration, can be swiftly applied in all hospitals without extensive additional scrutiny.

Finally, it should be realised that even with all the efforts as described in this thesis, hazards to patient safety cannot be fully eliminated. The purpose of a *clinically driven approach* and of a *prospective risk inventory* should be to reduce the number of possible hazards. To quickly identify residual hazards after the implementation of new instruments in clinical practice a post-market surveillance system should be installed. Currently, the registration of complications is only mandatory in research settings. In addition, this surveillance system should proactively intervene in case a trend is registered regarding an increase in adverse effects after a new instrument is implemented.

Finally, although not a research topic in this thesis, it is apparent that the safety of new surgical devices in daily clinical practice can only be warranted by proper handling. Therefore, education and training should be mandatory for every new user.

By identifying and reducing hazards before new technology is implemented together with an early identification of adverse effects after its implementation, a serious step can be taken to safer innovation in health care.



SCALE 2:1

Summary / Samenvatting

12

Summary

This thesis was initiated to explore different methods that can be used during the pre-clinical stage of the development of surgical innovations, more specifically new medical devices. Ideally, major hazards to patient safety are eliminated before these innovations are tested in human subjects. We used laparoscopic hysterectomy as a starting point for this thesis. The research questions in this thesis were approached from both a clinical as well as a technical point of view. Two concepts were assessed: the *clinically driven approach* to enhancing surgical instruments or techniques and the *prospective risk inventory* of new technology before its introduction in daily clinical practice.

Clinically driven approach

In **chapter 2** we established that during total laparoscopic hysterectomy (TLH) the colpotomy step (meaning the separation of the vagina from the cervix, typically the final step of TLH) is regarded as the most difficult and time consuming step by specialists in minimally invasive gynecologic surgery (MIGS). This was substantiated by the measurements of operation time and colpotomy time. The long duration of the colpotomy step was even more pronounced with increasing BMI. In close cooperation with engineers from the University of Technology, Delft The Netherlands, these findings resulted in a proposal for the vaginal approach to the colpotomy step with the aid of a new uterine manipulator.

To explore the required characteristics that the envisaged prototype should meet, a literature review was performed in **chapter 3.** The shortcomings of existing manipulators were used to improve the prototype. It was found that few manipulators offer lateral movement of the uterus, whereas at the same time this movement is regarded as important during ligation of the uterine arteries. Surprisingly, little evidence was found regarding the efficacy of uterine manipulators even though currently the use of these instruments during TLH is regarded as standard procedure.

After the results from chapter 3 were incorporated in the prototype, a model to test the functionality of the prototype was searched. On account of positive experiences with the use of human cadavers for teaching purposes, in **chapter 4** we decided to assess human cadavers as a model for testing new surgical instruments. Serious shortcomings in the design of the prototype were revealed that were not noticed during previous in-vitro tests in training-box models. As such, the cadaver tests added essential information to the developmental phase of the manipulator. However, significant limitations were encountered of cadavers as models due to anatomical shortcomings that prevent cadavers from being used on a larger scale for the purpose of testing new medical devices.

Next, the current controversies regarding the use of power morcellators in laparoscopic hysterectomy and myomectomy were addressed. Tissue spillage, which occurs when tissue is morcellated in the abdominal cavity, most likely leads to upstaging of disease in case of the presence of an occult uterine malignancy (more specifically uterine sarcoma). To overcome the problems regarding tissue spillage, **chapter 5** and **chapter 6** examined the onset and characteristics of tissue spillage during morcellation and instrument characteristics that could influence this onset. Torque was found to be the cause of tissue spillage. Furthermore, we found that during the majority of the procedure (60%) only small particles were created which are easily subjected to torque. Also, the amount of tissue spillage was not linearly related to uterine weight, suggesting that after a certain point the risk of tissue spill increases significantly. Finally, it was found that larger diameters of the morcellation instruments (up to 20mm) and an oscillating blade rather than a rotational mechanism all decreased the amount of spill.

The findings from chapter 5 and 6 were used to enhance the current morcellation mechanism. In **chapter 7** a prototype is discussed that resolves the problem regarding torque. Inspired by the lamprey, a fish resembling eels that use their teeth and suction to attach themselves to other fish and feed of their blood, an instrument was developed with similar teeth that fixate the morcellated tissue as it is inserted in the teeth-lined instrument. As such, it prevents the uncontrollable rotation of tissue fragments due to torque, thereby reducing tissue spillage.

Prospective Risk Inventory

A prospective risk inventory (PRI) is an important item of a safety management system and intends to foresee risks in health care processes rather than to remedy adverse events after they have occurred. The PRI is an important part of the *Leidraad Nieuwe Interventies in de Klinische Praktijk*, which was published in 2014. In this thesis, the concept of the PRI is applied to further enhance the morcellation procedure.

To better understand the risks of morcellation in daily practice, in **chapter 8** we established the risk of encountering unexpected uterine leiomyosarcoma (ULMS) during surgical procedures for presumed benign pathology. The risk of ULMS in women undergoing surgery was 1:385 or 0.26% for the whole group, and 1:795 or 0.13% for unexpected ULMS. Moreover, the risk for receiving non-standard treatment for ULMS (meaning abdominal hysterectomy with or without bilateral oophorectomy) in the unexpected group was even lower at 0.03% or 1:3333 patients. In addition, it was demonstrated that women aged 40-50 years of age presenting with abnormal uterine bleeding (AUB) are most at risk for unexpected ULMS. Moreover, ULMS are rare in women under 40 years of age.

To solve the occurrence of tissue spillage into the abdominal cavity, morcellation within a collection bag, or *in-bag* morcellation, is increasingly regarded as the new standard for morcellation. However, the evidence regarding the oncological safety and efficacy is lacking. In **Chapter 9** the rationale behind in-bag morcellation for myomectomy specimens was examined. It was hypothesized that tissue spillage occurs regardless of in-bag techniques. Indeed, we demonstrated that myoma cells are spilled into the abdomen even before morcellation is performed. Reducing the risks of tissue spillage in myomectomy is therefore limited, even with the in-bag morcellation technique.

The PRI of in-bag morcellation was finalized in **chapter 10.** A Health Failure Mode and Effects analysis (HFMEA) was performed to prospectively identify moments in the morcellation procedure that are at risk for tissue spill. The main finding was that although the spillage of larger particles can be avoided, the risk of spillage of small particles or microscopically amounts of spill remains due to contamination of instruments that came into contact with the morcellated tissue. The clinical consequences of macro- versus micro-spillage are yet unknown. Secondly, requirements of morcellation bags are defined to minimize the occurrence of tissue spillage. Only materials should be used that can withstand forces applied during power morcellation, including instrument and tissue manipulation, as well as pressure and airflow caused by insufflation of the bag. In addition, bags should remain impermeable to tissue cells under these conditions. Finally, the design of containment bags should be able to accommodate the camera, morcellator and possibly a third instrument in the bag so that the iatrogenic puncture of bags can be avoided.

In conclusion, this thesis assessed different methods that can be used to examine the safety of new medical technology during the early pre-clinical stage of surgical innovations. The combination of a *clinically driven approach* to difficulties from daily clinical practice with the *prospective risk inventory* resulted in prototypes of surgical instruments that better meet the demands of clinical practice and allowed an early identification of patient safety hazards of the instruments that were used as a template in this thesis.

Samenvatting

Dit proefschrift heeft verschillende methoden onderzocht die gebruikt kunnen worden om risico's van nieuwe chirurgische instrumenten op het gebied van patientveiligheid te evalueren alvorens hun introductie in de klinische praktijk. Idealiter worden deze risico's herkend en waar mogelijk geëlimineerd voordat de klinische testfase aanvangt. De laparoscopische hysterectomie (LH) diende hiervoor als uitgangspunt. Het onderzoek werd zowel vanuit een medisch klinisch, als vanuit een technisch oogpunt bekeken. Twee concepten werden geëvalueerd: de *kliniek-geïniteerde* benadering voor het ontwikkelen van nieuwe technieken of instrumenten, en de *prospectieve risico inventarisatie* van nieuwe technologie voordat deze in de praktijk wordt geïntroduceerd.

Kliniek-geïnitieerde benadering

In **hoofdstuk 2** stelden we vast dat tijdens LH de colpotomie stap (het separeren van de vagina en cervix, doorgaans de laatste stap waarna de uterus kan worden verwijderd) door specialisten in minimaal invasieve gynaecologische chirurgie (MIGC) wordt gezien als de moeilijkste en meest tijd rovende stap van de procedure. Dit werd onderbouwd door onze metingen van de colpotomie tijd en totale operatieduur. Tevens werd een sterke positieve correlatie gevonden tussen de colpotomie duur en *Body Mass Index*. De resultaten uit dit hoofdstuk werden gebruikt om samen met ingenieurs van de Technische Universiteit Delft een prototype te ontwikkelen van een uterus manipulator waarbij de colpotomie middels een vaginale benadering kan worden uitgevoerd.

Om de eigenschappen te bepalen voor de nieuwe uterusmanipulator, werd in **hoofdstuk 3** de bestaande literatuur over dit onderwerp onderzocht. De tekortkomingen van bestaande manipulatoren werden gebruikt om het prototype te verbeteren. Slechts weinig bestaande manipulatoren bieden een onafhankelijke laterale beweging van de uterus, terwijl deze beweging juist als belangrijk wordt beschouwd tijdens het coaguleren van de arteriae uterinae. Opvallend weinig bewijs werd gevonden met betrekking tot de effectiviteit van deze manipulatoren, ondanks dat het gebruik ervan wordt gezien als standaard procedure.

Na optimalisatie van het prototype werd vervolgens een model gezocht voor de eerste testfase. Gebaseerd op de positieve resultaten van het gebruik van humane kadavers voor educatieve doeleinden (zoals het aanleren van chirurgische procedures), werd in **hoofdstuk 4** het gebruik van humane kadavers als model voor het testen van nieuwe chirurgische instrumenten geëvalueerd. Hierbij kwamen serieuze tekortkomingen van het prototype naar voor, welke niet gezien werden bij voorgaande in-vitro testen in een laparoscopische oefenbox. De testen in het humane kadaver model brachten dus essentiële informatie aan het licht. Echter, door anatomische tekortkomingen van de

verschillende kadavers werd het gebruik ervan op grote schaal voor het ontwikkelen van nieuwe chirurgische instrumenten niet geschikt geacht.

Vervolgens werden de controverses met betrekking tot het gebruik van *power morcellatoren* tijdens LH en laparoscopische myomectomie (LM) onderzocht. Tijdens morcelleren worden kleine weefselfragmenten gemorst in de buik (weefsel spill). In de aanwezigheid van een niet onderkende maligniteit, in het bijzonder een sarcoom van de uterus, is er door weefsel spill kans op verslechtering van de prognose van de patiënt. Om het optreden van weefsel spill beter te begrijpen, werd in **hoofdstuk 5 en hoofdstuk 6** het optreden van dergelijke spill en factoren die hierop van invloed zijn onderzocht. Tevens werd de invloed van eigenschappen van het instrument op het optreden van spill onderzocht.

Torque bleek de oorzaak van het optreden van spill. Gedurende het grootste gedeelte van de procedure (60%) werden slechts kleine fragmenten gecreëerd door de morcellator en deze kleine fragmenten waren gevoelig voor torque. Er was geen lineair verband tussen de hoeveelheid spill en het gewicht van de uterus, wat suggereert dat er een afkappunt is, waarbij de hoeveelheid spill significant toeneemt. Tot slot stelden we vast, dat minder spill optreedt bij het gebruik van morcellatoren met een grotere diameter (20mm) en bij het gebruik van een oscillerend mes in plaats van een roterend mes.

De bevindingen uit hoofdstuk 5 en 6 werden gebruikt om het mechanisme van de huidige morcellatoren te verbeteren. In **hoofdstuk 7** werd een prototype gepresenteerd dat het probleem van torque oplost. Het prototype werd gebaseerd op de prik, een vis die tanden en zuigkracht gebruikt om zich te bevestigen aan andere vissen en zich voedt met hun bloed. In de schacht van het prototype zijn tanden bevestigd welke het gemorcelleerde weefsel grijpen en fixeren, waardoor er geen torque optreedt en spill voorkomen kan worden.

Prospectieve Risico Inventarisatie

Een prospectieve risico inventarisatie (PRI) is een belangrijk onderdeel van een veiligheidsmanagementsysteem en heeft als doel potentiële risico's in (gezondheids) processen te voorkomen, in plaats van schade te herstellen nadat deze is opgetreden. De PRI is een belangrijk onderdeel van de Leidraad Nieuwe Interventies in de Klinische Praktijk, welke is gepubliceerd in 2014. Het concept van de PRI werd in dit proefschrift toegepast om de morcelleer techniek te verbeteren.

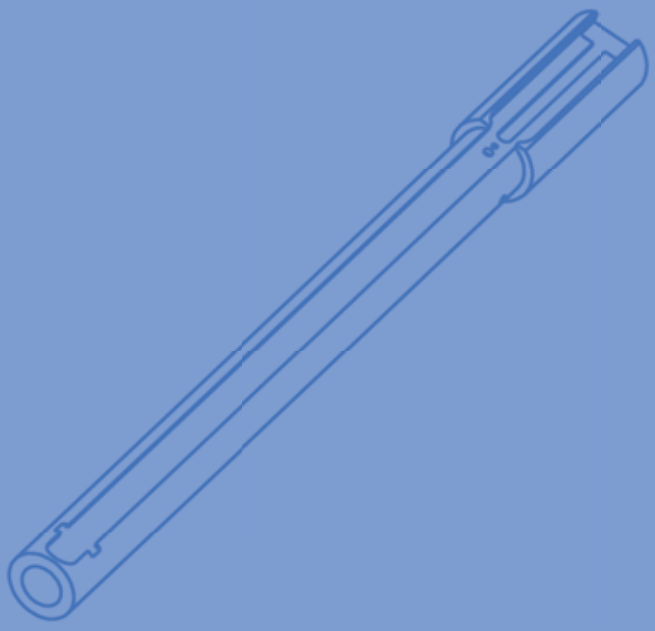
Om het risico van morcelleren beter in te kunnen schatten, werd in **hoofdstuk 8** de kans vastgesteld op het aantreffen van een (onverwacht) uterussarcoom tijdens operatieve ingrepen wegens verondersteld benigne pathologie. Het risico voor vrouwen die een

dergelijke ingreep ondergingen op een uterussarcoom bleek 1:385 of 0.26% voor de gehele groep, en 1:795 of 0.13% voor onverwachte uterussarcomen. Vrouwen in de leeftijd tussen 40-50 jaar met abnormaal uterien bloedverlies hadden de grootste kans op een onverwacht uterussarcoom. Onder de leeftijd van 40 jaar was een uterussarcoom zeldzaam.

Om te voorkomen dat tijdens morcelleren spill optreedt, wordt het morcelleren in een zak (*in-bag* morcelleren) in toenemende mate gezien als nieuwe goudstandaard voor deze procedure. Echter, de oncologische effectiviteit en veiligheid van deze nieuwe techniek is nog niet bekend. In **hoofdstuk 9** werd de rationale voor het in-bag morcelleren na LM geëvalueerd. Onze hypothese was, dat spill tijdens LM al optreedt alvorens het myoom in de zak wordt gemorcelleerd. Er werden inderdaad al myoomcellen aangetroffen in de buik, nog voor het weefsel werd gemorcelleerd. Het reduceren van spill bij LM is daarom zelfs met in-bag morcelleren beperkt.

De PRI van in-bag morcelleren werd afgerond in **hoofdstuk 10**. Een *Health Failure Mode and Effects Analysis* (HFMEA) werd verricht om prospectief de risico's van het in-bag morcelleren met betrekking tot het optreden van spill te identificeren. Hoewel de spill van grotere stukken weefsel kan worden voorkomen, blijft het risico op spill van heel kleine stukjes of microscopische deeltjes aanwezig door contaminatie van de gebruikte instrumenten met het gemorcelleerde weefsel. Echter, op dit moment is niet bekend wat de klinische consequentie is van spill van grote danwel kleine weefselpartikels. Verder werden op basis van deze studie materiaaleisen van de morcelleerzakken geformuleerd. De zakken dienen bestand te zijn tegen de krachten die worden toegepast op de zak, zoals tijdens weefselmanipulatie of door het opblazen van de zak met CO2 gas. Bovendien moet het materiaal onder al deze omstandigheden impermeabel voor cellen blijven. Tot slot moet de zak een opening bieden voor de camera, de morcellator en wellicht een derde instrument om te voorkomen dat de zak dient te worden geperforeerd.

Concluderend, heeft dit proefschrift verschillende methoden geëvalueerd die gebruikt kunnen worden om de veiligheid van nieuwe medische technologie te onderzoeken in de vroege pre-klinische fase van de ontwikkeling. De *kliniek-geïnitieerde benadering* van nieuwe chirurgische instrumenten resulteerde in prototypes die voldoen aan de vraag uit de kliniek. De *prospectieve risico inventarisatie* maakte een vroegtijdige identificatie mogelijk van potentiële risico's op het gebied van patiëntveiligheid van de chirurgische instrumenten die dienden als uitgangspunt in dit proefschrift..



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Curriculum Vitae

Lukas van den Haak was born on November 19th 1979 in Dongen, The Netherlands. Parallel to his secondary education at the St-Oelbertgymnasium in Oosterhout, he attended preparatory dance courses at the Rotterdam Dance Academy.

After graduating in 1998, he enrolled at the Royal Conservatory in The Hague to study classical dance. In 2000 he won the "Aanmoedigingsprijs Stichting Dansersfonds '79", a scholarship awarded to promising students of dance in The Netherlands. That same year he was invited to study at the National Ballet School in Toronto Canada and the Canadian National Ballet. In 2001 he received his Bachelor of Arts degree from the Royal Conservatory in The Hague.

In 2002 he started medical school at the University of Leuven in Belgium, receiving his Master of Science degree in 2007. For his internships, he transferred to the Leiden University The Netherlands, where he received his Medical Degree in 2010.

He then started as a physician (ANIOS) at the department of Obstetrics and Gynecology at the Haaglanden Medisch Centrum The Hague (dr. M.J. Kagie). During this period he started research on surgical treatments of cervical cancer under supervision of dr. de Kroon. In January 2012, he started his residency at the Haaglanden Medisch Centrum (dr. M.J. Kagie) and the Leiden University Medical Center (prof. dr. J.M. van Lith). In October 2013 he entered a PhD program at the department of Gynecology (section Minimally Invasive Surgery) at the Leiden University Medical Center under supervision of prof. dr. F.W. Jansen.

In June 2016 he recommenced his residency and he currently works at the Leiden University Medical Center to finish his residency.

Dankwoord

Dit proefschrift is tot stand gekomen met behulp van velen. Graag wil ik iedereen bedanken die betrokken is geweest bij dit onderzoek, in het bijzonder ook alle personen die betrokken waren bij de ontwikkeling van MobiSep. De volgende personen bedank ik graag afzonderlijk.

Frank Willem, ik heb enorme bewondering voor de manier waarop jij je promovendi op waarde weet te schatten en hen tegelijk in hun waarde weet te laten. Door jouw manier van begeleiding heb ik kunnen groeien als persoon.

Johann, zonder jouw idee en uitwerking van de MobiSep was dit proefschrift er niet geweest. Het was fijn samenwerken en ik kijk met veel plezier terug op onze overleg momenten in je keuken met de hond aan mijn voeten.

Bertho, ik heb veel geleerd van je wetenschappelijke kijk op onze klinische testen en de artikels die hieruit zijn voortgekomen. Ondanks de geografische afstand, heb je je steeds als een heel betrokken co-promotor getoond.

Cor, bij jou is het enthousiasme voor het verrichten van wetenschappelijk onderzoek begonnen. Wat fijn dat je betrokken kon blijven bij dit proefschrift.

De endo-club, voor de wetenschappelijke kruisbestuiving, tips & tricks en de sociale activiteiten.

Mede onderzoekers **Mathijs, Linda, Edith, Inge, Suus, Femke, Joost, Ada, Tess, Kim en Jeroen** voor de noodzakelijke ontspanning tijdens het harde werken op de J7 en K6

Alle **wetenschapsstagestudenten** en ANIOS die mij bij mijn onderzoek hebben geholpen.

John, Jenny, Ewout, met veel plezier kwam (en kom!) ik naar de TU Delft voor altijd leerzame, maar vooral ook leuke en gezellige overleg momenten. Ik heb veel bewondering voor jullie ingenieurs-blik op onze medische problemen.

Saar en Eef, stelling 11: al het goede komt in drieën! Wat was mijn onderzoekstijd zonder jullie geweest? We grappen nog wel eens dat er een soort 'magie' is geweest op de K6. Ons fotobord spreekt boekdelen. Naast alle gezelligheid heb ik op wetenschappelijk vlak ontzettend veel van jullie geleerd. Ik kan me dit proefschrift zonder jullie input niet voorstellen. Ik kijk uit naar al onze komende servettendiners!

Joost en An, alle drie werkten we ongeveer tegelijk aan ons proefschrift. An gaf recent als eerste het goede voorbeeld met haar promotie. Joost, nu is het aan ons! Ik ben ontzettend trots dat ik peter van Céline mag zijn, en (suiker)oom van Mathis!

Schoonouders, Rinus en Meggie, voor jullie continue interesse in en betrokkenheid bij mijn onderzoek en werk.

Zusje, de manier waarop jij steeds een positieve kijk op het leven weet te houden, heeft mij helpen doorzetten bij de moeilijke momenten in mijn opleiding en onderzoekstijd.

Emillia, mijn "halve" dochter! Wat heerlijk dat je zo betrokken bent in ons leven. Je gaat nu zelf studeren, ik kan niet wachten tot de zoete inval in Utrecht!

Papa, ik weet zeker dat je mijn onderzoek geweldig interessant zou hebben gevonden. Ik heb vaak gedacht wat jouw oplossing voor bepaalde vraagstukken zou zijn geweest.

Mama, mijn successen waaronder dit proefschrift heb ik voor een groot deel aan jou te danken. Steeds heb je de lange termijn in het oog gehouden, ook op de momenten waarop ik dat nog niet kon. Wat ben ik achteraf blij dat je ervoor hebt gezorgd dat de weg om arts te worden open bleef.

Bart, dank voor al je onvoorwaardelijke liefde, advies en steun, bij elk pad dat ik kies. Je zorgt voor de glans op de behaalde successen in dit onderzoek, in mijn werk als arts en in ons leven samen.