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Reduced morbidity by using LigaSure compared to conventional inguinofemoral lymphadenectomy in vulvar cancer patients: A randomized controlled trial

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ABSTRACT

Background: Inguinofemoral lymphadenectomy (IFL) is part of the surgical treatment of different malignancies of the genital tract and/or the lower limb including vulvar carcinoma, penile carcinoma and melanoma. IFL is associated with morbidity in up to 85% of the patients. The aims of this MAMBO-IC study (Morbidity And Measurement of the Body) are to study the feasibility of using LigaSure for IFL and to assess the differences in the incidence of short-term complications using LigaSure versus conventional IFL randomized within each individual patient.

Methods: In this multicenter randomized controlled trial (RCT), women diagnosed with squamous cell carcinoma of the vulva with an indication for bilateral IFL were included. It was randomly assigned for which groin the LigaSure was used; the other groin was treated with conventional IFL (sharp/diathermia). We estimated the incidence of ≥1 complication(s) per groin using logistic regression and compared this between the two surgical methods, adjusting for possible confounders.

Results: We included 40 groins of 20 patients. The estimated incidence of ≥1 complication(s) was 29% after LigaSure versus 70% after conventional IFL (risk difference 41% (95% CI 19–62), $p < 0.001$). Patients' reported restriction of daily living activities and maximum pain score were equal for both treatment methods. There were no differences in the surgeon reported workload scores.

Conclusions: This RCT shows that LigaSure for IFL is feasible and associated with significantly less short-term surgical complications compared to conventional IFL. Further studies with a larger sample size are needed to validate our findings. ISRCTN15057626.

Synopsis

Ligasure for inguinofemoral lymphadenectomy is feasible and significantly reduces short-term morbidity compared to conventional surgery in women with vulvar cancer.

1. Introduction

Inguinofemoral lymphadenectomy (IFL) is part of the surgical treatment of malignancies of the genital tract and/or the lower limb such as vulvar carcinoma, penile carcinoma and melanoma. This procedure is associated with surgery related morbidity in up to 85% of the patients. This morbidity concerns short-term (wound infection, formation of lymphoceles, wound breakdown) and long-term morbidity (lymphedema, cellulitis, erysipelas) [1–4]. Advanced age and comorbidity including diabetes are risk factors for postoperative complications after IFL [3,5,6].

We have demonstrated in two consecutive national prospective studies 'Morbidity And Measurement of the Body' (MAMBO-IA and IB) that volume-controlled drainage (drain removal if production is < 30

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ml/day with a minimum of three days) of the groin resulted in a reduced short-term complication rate when compared to short drainage (drain removal on day five regardless production). Nevertheless, complications are still present in 67% of the patients after volume-controlled drainage, and 53% of these patients needed to be readmitted to the hospital [7]. As a consequence, these complications lead to a significant increase in health care costs, which supports the urgent need for additional effort to reduce surgical morbidity.

Adaptations in the surgical approach may play a key role in reducing morbidity associated with IFL. Several modifications in the surgical approach have been explored, such as separate incisions, unilateral IFL, sparing of saphenous vein, preservation of the fascia lata and continuous skin closure, but only a limited reduction of morbidity was achieved [8,9]. Last decade, new surgical devices have been developed including: energy-based ultrasonic, bipolar vessel or electrothermal vessel sealing. These devices can seal blood and lymph vessels, and may subsequently reduce postoperative leakage of lymph fluid which may reduce surgical morbidity. Although these new surgical devices are increasingly used in clinical practice in addition to conservative surgery (sharp knife dissection, mono- or bipolar electrocautery), comparative studies are limited.

There are no studies comparing Ligasure and conventional IFL in vulvar cancer patients. RCTs comparing LigaSure versus conventional axillary dissection in breast cancer patients reported significant less intra-operative blood loss, reduction in the amount of drained lymph fluid, less days of suction drainage and shorter hospitalization in patients treated using LigaSure. No differences were reported in the rate of hematomas, reoperations or infections [10–12].

In the current RCT (MAMBO-IC) we aim to study the feasibility of LigaSure for IFL and to assess the incidence of short-term complications, using LigaSure versus the conventional performance of IFL randomized within each individual patient. Moreover we will evaluate patients' and surgeons' experience.

2. Methods

2.1. Patients

We conducted this RCT, the MAMBO-IC study (MAMBO: Morbidity And Measurement of the BOdy), in two gynecologic oncology centers: the Radboud university medical center and the University Medical Center Groningen. All patients aged ≥18 years with vulvar squamous cell carcinoma (SCC) with an indication for bilateral IFL were eligible for inclusion. Patients were excluded if they received radiotherapy to the vulva, groins and/or pelvis previously, pelvic lymphadenectomy, or if there was an indication for IFL with the 'en bloc' approach or other histology than SCC. Patients were informed about this study and approached to participate during a regular visit at the outpatient clinic. Written informed consent was obtained from all included patients before enrollment. We aimed to include 20 patients and 40 groins.

The study was conducted according to the principles of the Declaration of Helsinki (2008) and to the Medical Research Involving Human Subjects Act (Dutch: WMO). The study protocol was medical-ethically approved to be conducted by the Medical Ethical committee of Arnhem-Nijmegen (NL62326.091.17), and registered in the ISRCTN registry (ISRCTN15057626).

2.2. Randomization process

Patients were randomized to the intervention (LigaSure™ Small Jaw Open Sealer/Divider LF1212A (Medtronic)) for either the left or right groin with a 1:1 allocation ratio. We used a variable block randomization method, with a block division of 2, 4 using Castor EDC. The outcome of randomization was blinded for the patients, doctors, nursing staff and caregivers, except for the performing surgeons.

2.3. Surgical procedure

All patients underwent a bilateral IFL. The LigaSure devices were partly provided by the manufacturer. It was randomly assigned for which groin the LigaSure was used to perform this surgical procedure and for the other groin, the conventional method (scalpel and/or electrocautery) was used. Preoperative antibiotic prophylaxis consisted of 2000 mg Cefazoline and 500 mg Metronidazole intravenously. The IFL was a standard procedure as described previously [13]:the surgical technique consist of separate incisions parallel to the inguinal ligament. The incision is carried through the subcutaneous tissues to the superficial fascia. The latter is incised, and the fatty tissue between it and the fascia lata is removed over the femoral triangle. The dissection is carried 2 cm above the inguinal ligament to include all the inguinal nodes. The saphenous vein is preferably preserved. The fascia lata is then split longitudinally over the proximal femoral vein, and the fatty tissue containing the femoral lymph nodes is removed. There is no need to remove the fascia lata lateral to the femoral vessels and no need to perform a sartorius muscle transposition. A high vacuum Redon drain (775 mmHg, 0.9 bar negative pressure) was placed in the groin just before closure. IFLs were performed either subsequently by the same surgeon or, to reduce operating time, simultaneously by two different surgeons.

2.4. Postoperative care

The groin drain was removed when the production of the drain is < 30 ml/day with a minimum of two days, according to the MAMBO-IA protocol [7]. After each surgical procedure, the surgeon was requested to complete the online questionnaire regarding their experience regarding the surgical procedure containing SURG-TLX [14]. In the SURG-TLX, surgeons rate six dimensions of workload: mental-, physical- and temporal demands, task complexity, situational stress, and distractions, on a 20-point Likert scale, anchored between low and high.

2.5. Follow-up

Follow-up for the study was completed eight weeks after surgery. Patients were routinely seen at two and eight weeks after surgery by a gynecologic oncologist, both groins were examined and any complication was reported. The gynecologic oncologist and other caregivers were blinded, except the gynecologic oncologist who performed the surgical procedure. All included patients were approached at eight weeks postoperatively by the investigator to complete a telephone questionnaire regarding pain and restriction of daily activities. The maximum postoperative pain and the restriction of daily activities was scored on a visual analogue scale (VAS) between zero (low) and ten (high).

2.6. Outcomes

The primary objective was to study the feasibility of LigaSure and to determine the incidence of any short term complication i.e.: wound breakdown and/or wound infection and/or lymphocele, within eight weeks after IFL after using LigaSure or the conventional method. Wound breakdown was defined as every spontaneous disrupted groin wound > 2 cm, wound infection as purulent exudates and/or positive culture and/or erythema and lymphocele as the collection of lymph fluid > 5 cm.

The secondary objectives were to determine the differences between the two surgical methods in duration of drainage and volume drained, operating time, to evaluate patients' experience regarding postoperative pain and restriction of daily activities, and to evaluate the surgeon's experience of both surgical procedures using a questionnaire.

2.7. Statistical analysis

The incidences of wound infection, primary wound dehiscence and

lymphocele are displayed by frequencies and compared with the McNemar test. To estimate the incidence of ≥1 complication per groin, we used a generalized linear model with a logit link and a binomial distribution, and a random effect for patient. In order to quantify the differences between conservative IFL and Ligasure, risk differences were estimated using this model, adjusted for the number of lymph nodes removed per groin. Continuous variables are summarized using the median and range and compared between the two treatments using the Wilcoxon Signed-rank test. Discrete variables were described by frequencies. Two-sided p-values <0.05 were regarded as statistically significant. Analyses were performed using SPSS version 22.0 [15].

3. Results

Twenty patients with 40 groins were included and randomized in this MAMBO-IC study; ten patients were allocated to IFL with LigaSure in the left groin and ten patients to IFL with LigaSure in the right groin, see Fig. 1. The IFLs were performed between October 2017 and October 2018 in either the Radboudumc (N = 9) or the University Medical Center Groningen (N = 11). Patient- and tumor characteristics are shown in Table 1, and did not notably differ between the two treatment centers. The indication for bilateral IFL was a tumor with a diameter of more than 4 cm in eight (40%) patients, pathologically proven lymph node metastases in five patients (25%), a positive SLN in three patients (15%) or local recurrent disease (without earlier IFL in primary treatment) in four patients (20%). In 17 patients, the IFL was performed concomitantly with vulvar surgery, and in three patients there was a positive SLN in the treatment of the current primary carcinoma and IFL was performed in a second procedure ranging between 34 and 60 days after the SLN procedure. The IFLs were performed by 11 different surgeons without differences in the applied standardized surgical technique, the number of dissected groins per surgeon ranged between one and 11.

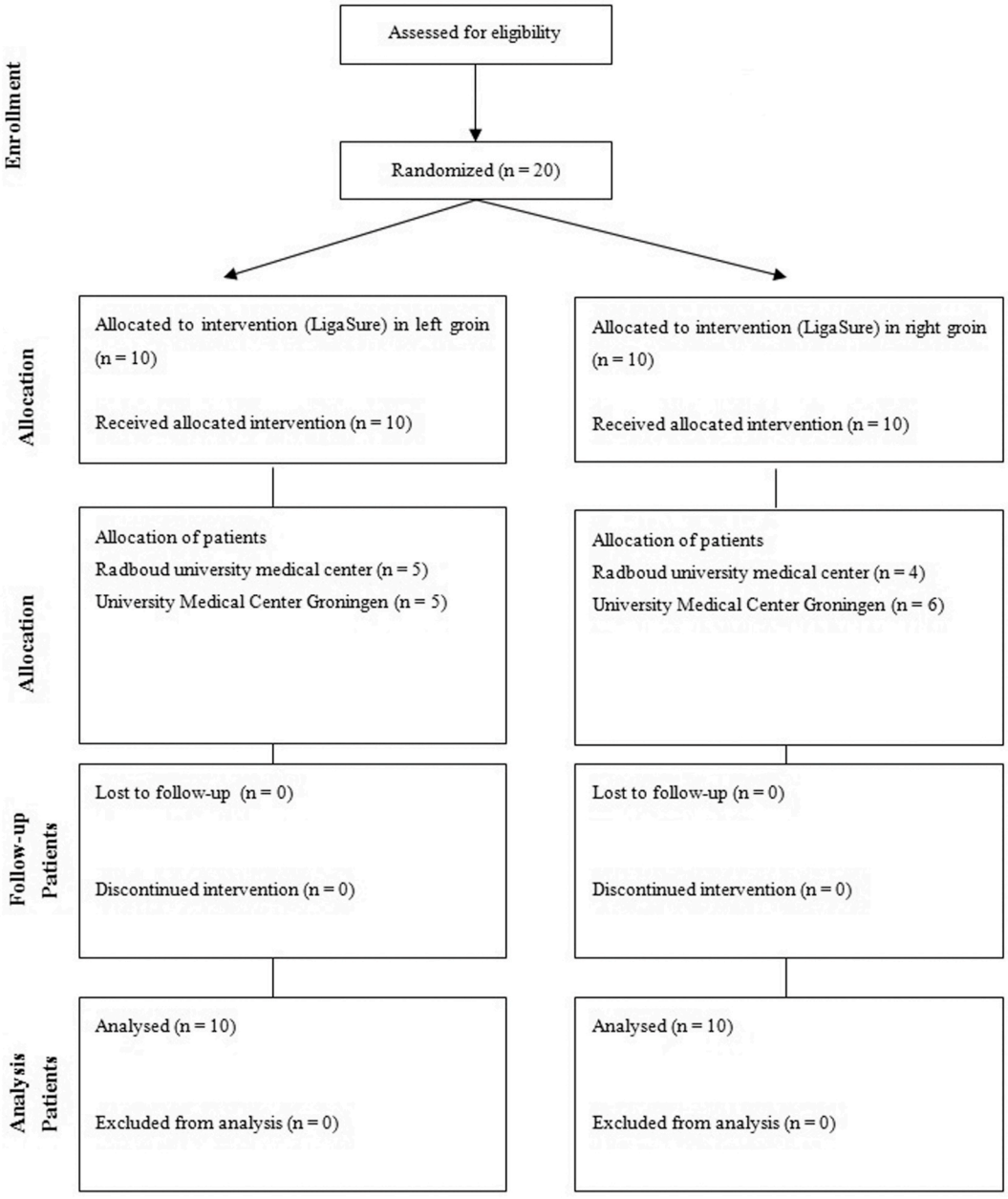

Fig. 1. CONSORT flowchart.

Table 1
Patient- and tumor characteristics of the study population.

	Median (range)	N (%)
Patient characteristics		
Age (years)	75 (53–88)	
Body mass index (kg/m^2)	29.3 (22.5–42.0)	
Diabetes Mellitus		
Yes		3 (15)
No		17 (85)
Smoking		
Yes		3 (15)
No		13 (65)
unknown		4 (20)
Tumor characteristics		
Diameter (mm)	37.5 (9–80)	
Location tumor		
Central		19 (90)
Lateral		2 (10)
Depth of invasion (mm)	(1.7–21.0)	
Focality		
Unifocal		20 (100)
Multifocal		0 (0)
Lymphovascular space involvement		
Yes		6 (30)
No		13 (65)
Unknown		1 (5)
Pathological tumor free margins		
Yes		19 (95)
No		1 (5)
Presence of precursor lesion		
None		5 (25)
HSIL		0 (0)
LS		3 (15)
dVIN		5 (25)
dVIN and LS		7 (35)

3.1. Surgical outcomes

The median duration of the IFL was 56 min (range 27–105) for groins dissected with LigaSure and 57 min (range 36–90) for groins dissected conservatively, p = 0.570. The median number of lymph nodes removed per groin was 9.5 (range 2–18) in groins treated with LigaSure versus median 10 (range 5–14) in groins treated by the conservative IFL, p = 0.692. Operative characteristics are summarized in Table 2.

3.2. Postoperative outcomes

The duration of drainage did not differ between LigaSure compared to conservative IFL, median 16.5 days (range 5–54) versus median 19.5 days (range 4–34) respectively, p = 0.727. The median volume drained per day for each treatment group is displayed in Fig. 2. The total volume drained during the period of drainage was not significantly different between groins treated by LigaSure or conservative IFL, median 1037 ml (range 200–5030) and median 1533 ml (range 325–6020) respectively, p = 0.156.

In this study, groins were drained according the MAMBO-IA study protocol: groin drain was removed when the production of the drain is < 30 ml/day with a minimum of two days. Twenty-one groins (21/40, 53%) of the groins was drained according protocol. Six groins (6/21, 29%) were drained longer and 11 groins (11/21, 53%) shorter than the protocol described, mainly due to complications and/or technical difficulties. In four groins (4/21, 19%) the drain was removed in deviation with the protocol but unclear if drained longer or shorter. Analyzing only groins drained according protocol (N = 21), the total drain production was significantly lower in the groins treated by LigaSure compared to conservative IFL, median 1180 ml (range 750–2760) and median 1885 ml (range 1430–3340) respectively, p = 0.043 without a difference in the duration of drainage between the two treatment groups, p = 0.180.

Table 2
Operative characteristics of the included groins.

	LigaSure (N = 20)		Conservative (N = 20)		p-value
	Median (range)	N (%)	Median (range)	N (%)	
Duration of procedure (minutes)	56 (27–105)		57 (36–90)		p = 0.261
Method of closure					
Intracutanous		5 (25)		5 (25)	P = 1.00
Stitches and intracutanous		4 (20)		4 (20)	
Staples		11 (55)		11 (55)	
Previous SLN procedure					
Yes		7 (35)		4 (20)	p = 0.29
No		13 (65)		16 (80)	
Number of lymph nodes removed per groin	9.5 (2–18)		10.0 (5–14)		p = 0.92
Number of groins with lymph nodes metastases		9 (45)		7 (35)	p = 0.52
Number of groins with lymph node metastases with extranodal growth		3 (15)		4 (20)	P = 0.67

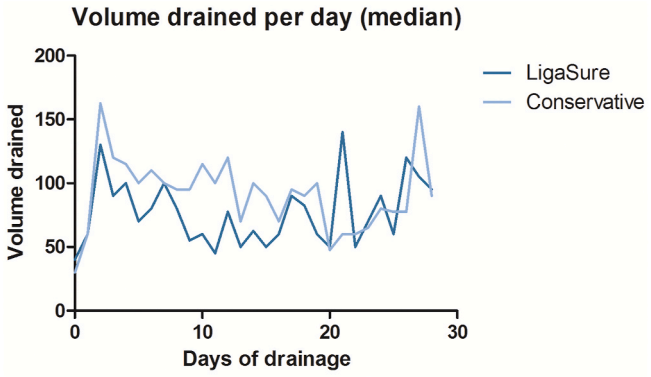

Fig. 2. Volume drained per day.

3.3. Short-term complications

The incidence of a wound infection, primary wound dehiscence and lymphocele per groin did not differ between the two surgical treatment methods. The estimated incidence of ≥1 complication per groin was 29% (95% CI 13–52) after LigaSure compared to 70% (95% CI 47–85) after conservative IFL (RD 41% (95% CI 19–62)), p < 0.001. See Table 3 for an overview of the outcomes.

One or more complications of the groin occurred in 70% (14/20) of the patients and are equally distributed between the two treatment centers. As shown in Fig. 3, in six patients a bilateral complication was present, and in eight patients an unilateral complication. In all patients with a unilateral complication, the groin in which the complication occurred was treated by conservative IFL. In conclusion, one or more complications were present in 14/20 (70%) of the groins treated with conservative IFL and in 6/20 (30%) in groins treated with LigaSure.

In 6/20 (30%) groins, treatment was necessary following a short-term complication after LigaSure. In groins treated with conservative IFL, treatment was given in 11/20 (55%) of the groins. Eight (8/20; 40%) patients were readmitted because of a complication of the groin with a median duration of 7.5 days (range 3–26). Four of these patients had a bilateral short-term complication of the groin, and four a unilateral complication. Secondary wound healing was reported in four groins

Table 3
(Estimated) incidence of short-term complications per groin.

Incidence of short-term complications per groin			
	Conservative N = 20	LigaSure N = 20	p-value
Wound infection	50%	30%	p = 0.125
Primary wound dehiscence	5%	5%	p = 1.0
Lymphocele	25%	20%	p = 1.0
≥1 complication	70%	30%	p = 0.0133
Estimated incidence of short-term complications per groin			
	Conservative	**LigaSure**	**Risk Difference (95% CI)**
≥1 complication[a]	70% (95% CI 47–85)	29% (95% CI 13–52)	41% (95% CI 19–62), p < 0.001

[a] Adjusted for number of lymph nodes removed.

of two patients. Adjuvant radiotherapy to the groins was given to 11/20 (55%) patients and postponed due to groin complications in 2/11 (18%) patients.

3.4. Surgeons' experience

Fig. 4 shows the workload scores for each dimension for both surgical methods. There were no notable differences in the surgeons' reported workload scores. Of the surgeons performing IFL using LigaSure, 75% had used this device previously. All surgeons who performed the conservative IFL would recommend this method to their colleagues, versus 15/20 (75%) surgeons who used LigaSure. Reasons for not recommending LigaSure to their colleagues were: conservative method is more easy, LigaSure is less precise compared to conventional IFL, prefers to use a combination of both LigaSure and the conservative method.

3.5. Patients' experience

Restriction of daily activities and maximum pain score were scored equally by the patients for both treatment groups. After LigaSure, the maximum pain score was median 3 (range 0–8) and after conventional IFL median 3 (range 0–9), p = 0.844. The restrictions of daily activities was scored median 0 (range 0–8) after LigaSure versus median 0 (range 0–8) after conservative IFL, p = 0.655.

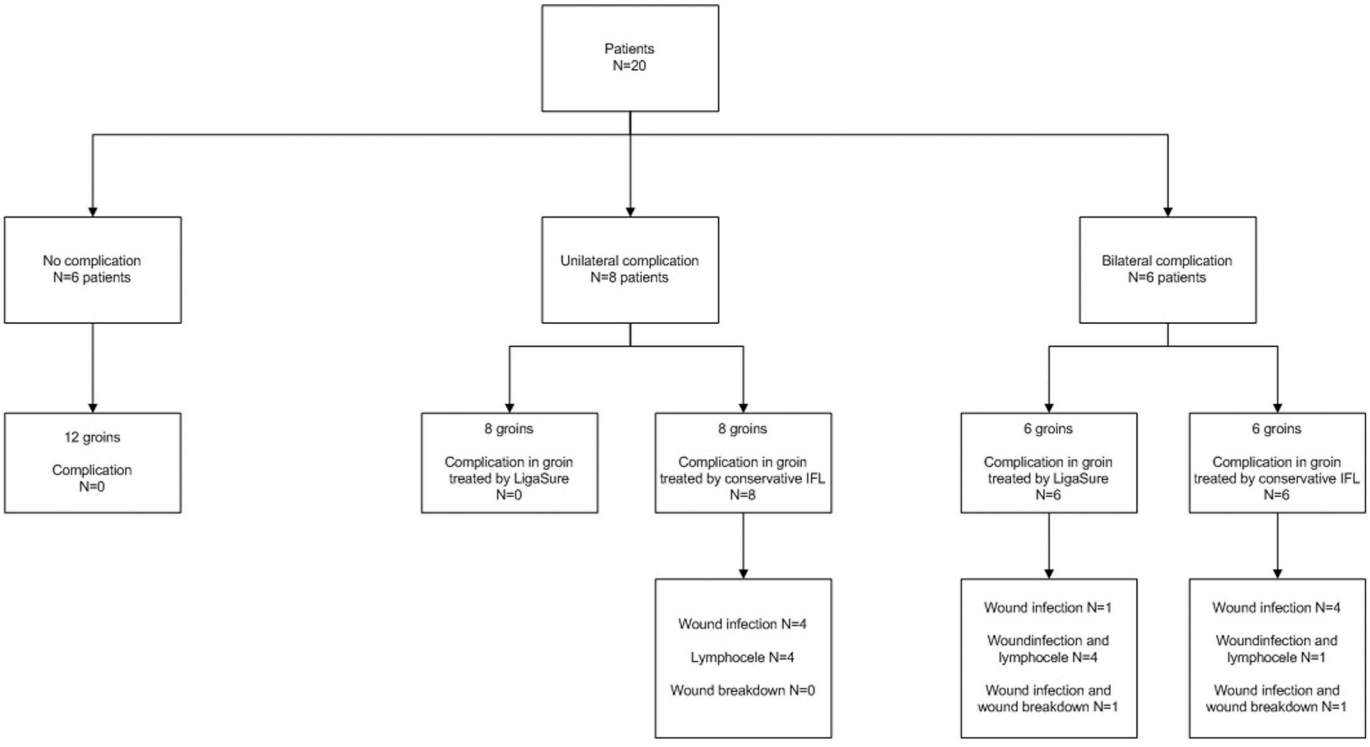

Fig. 3. Short-term complications of the groin stratified by surgical method used for IFL.

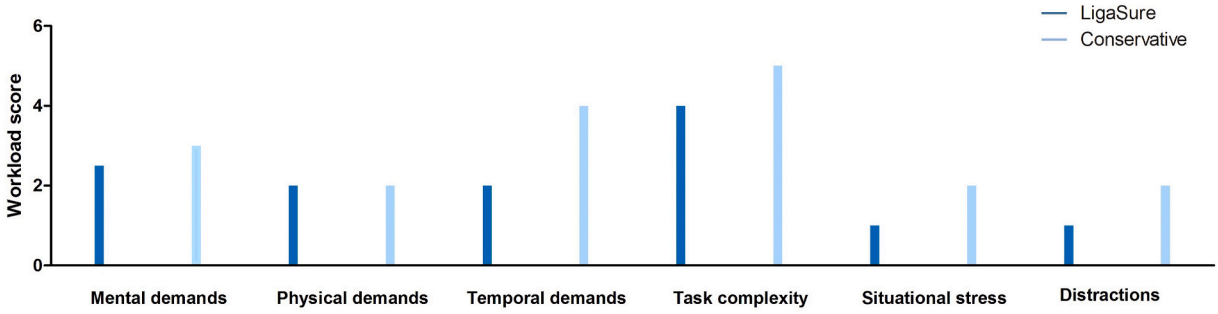

Fig. 4. Surgeons' workload score (median).

4. Discussion

4.1. Main findings

This multicenter RCT is the first study comparing LigaSure and conventional IFL in vulvar SCC patients. The use of LigaSure for IFL is feasible and significantly reduce the estimated incidence of ≥1 complication(s) per groin compared to conventional IFL. However, the incidence of a wound infection, primary wound dehiscence and lymphocele per groin did not differ between the two surgical treatment methods, probably due to lack of power. The duration of surgery, number of removed lymph nodes, duration of drainage and volume drained did not notably differ between the two surgical methods. In addition, the patients' and surgeons' experience did not differ between both treatment methods.

4.2. Interpretation

Although RCTs comparing LigaSure versus conventional axillary dissection in breast cancer patients reported reduced volume drained, shorter period of drainage and reduction of duration of postoperative hospital stay after LigaSure [10–12], this study did not confirm these results in vulvar SCC patients. However, in groins drained according protocol, the total drain production was significantly lower in the groins treated with LigaSure compared to groins treated with conservative IFL, without a difference in the duration of drainage. Due to our study design, with both treatments randomized within a patient, we were not able to assess the difference in days of hospital stay or readmission for the two surgical methods.

Using LigaSure, the simultaneous sealing and cutting of the vessels and tissue without the need of changing instruments might reduce the operating time. In breast cancer patients, the use of LigaSure for axillary lymphadenectomy significantly reduced the operating time with 15 min in a study including 100 women randomized for either LigaSure or conventional axillary lymphadenectomy [10].

In our study, there was no difference in operating time comparing Ligasure versus conventional IFL. In contrast, Pellegrino et al. [16] reported, in a study comparing the harmonic scalpel to conventional electrosurgery in 42 patients with vulvar cancer, a significant reduction of 25 min in operating time in favor of the harmonic scalpel. Operating time included radical local excision of the tumor combined with uni- or bilateral IFL. The reduction of operating time might be partially due to the use of the harmonic scalpel for the wide local excision of the vulvar tumor.

Although the introduction of the SLN procedure has become a big step forward in terms of reduced morbidity, IFL will always keep a place in the treatment of vulvar SCC patients, eg. in patients with a multifocal tumor and/or a diameter more than 4 cm. Therefore, attempts should be made to further reduce postoperative morbidity. In previous years, minimally invasive techniques are developed to reduce postoperative morbidity of IFL and promising results are published. A systematic review including nine retrospective studies and 249 video endoscopic inguinofemoral lymphadenectomy (VEIL) procedures reported a complication in 6% of the groins, including a lymphocele in 3.6%, wound infection in 1.2% and lymphedema in 0.4% of the groins [17]. Recently, an RCT, randomizing for either VEIL with the limb subcutaneous approach (N = 8) or with the hypogastric approach (N = 17), compared the postoperative morbidity to a historical cohort of 21 patients undergoing open IFL showed significantly less complications in the groin were reported after VEIL (infection 8% vs 19%, lymphocele 8% versus 10%, wound dehiscence or skin necrosis 0% versus 14%) [18]. In contrast, one study including 12 patients and 22 groins reported the rate of ≥1 complication after robot-assisted VEIL (VEIL-R): 59% per groin and 75% per patient [19]. In spite of the small number of patients, these complication rates are even higher compared to the rate of ≥1 complication in previously reported studies after open IFL [7,20]. In addition, none of the mentioned studies included Caucasian women, and neither reported data concerning the oncologic safety of this procedure. A large prospective trial with adequate follow-up of at least 2 years is needed to determine the oncologic safety of VEIL and to determine the postoperative morbidity in women with vulvar SCC. In addition, VEIL is preferably compared to open IFL using either a energy-based ultrasonic, bipolar vessel or electrothermal vessel sealing device, as the device used might be key to lowering postoperative morbidity.

Based on the results of this study, the use of LigaSure is feasible to perform IFL and the surgeons' workload was equal. However, treatment with LigaSure leads to additional costs (about €250/$285 per disposable device) compared to the less costly diathermia and/or scalpel. These additional costs are counterbalanced by reduced costs of postoperative care, such as treatment of complications and readmissions, as result of reduced surgical morbidity after IFL using LigaSure. Future research including a cost-effectiveness analysis may give the answer if LigaSure is cost-effective in the treatment of vulvar SCC patients.

4.3. Strengths and limitations

Besides the obvious limitation of a small number of included patients, the surgical procedures in our study were performed by different surgeons. However, this reflects daily clinical practice and shows that there is a very short learning curve. Another limitation is the follow-up of eight weeks after surgery. Therefore, long-term follow-up data is not available to evaluate long-term complications such as lymphedema.

The strengths of this study are the multicenter design, prospective nature and the randomization within a patient. Randomization within one patient results in the reduction of many patient-related potential confounders. In addition, another strength is the standardization of both the surgical procedure and postoperative drainage of the groin.

5. Conclusion

We demonstrated that LigaSure is feasible for IFL and shows promising results in terms of reduced postoperative morbidity compared to conservative IFL. Validation in a large cohort is needed to implement this new technique in clinical practice.

Declaration of competing interestCOI

None.

Author contributions

AP, HA, JP, JH contributed to conceptualization; AP, HA, JI, JP, JH contributed to methodology; AP, HA, CK, JI, JP, JH performed data acquisition; AP, JI, JP, JH performed analysis; AP, HA, CK, JI, JP, JH interpret the data for the work; AP, HA, CK, JI, JP, JH wrote the manuscript; AP, HA, CK, JI, JP, JH approved the final version to be published.

Details of ethics approval

This study was conducted according to the principles of the Declaration of Helsinki (2008) and to the Medical Research Involving Human Subjects Act (Dutch: WMO). The study protocol was medical-ethically approved to be conducted by the Medical Ethical committee of Arnhem-Nijmegen (NL62326.091.17), and registered in the ISRCTN registry (ISRCTN15057626). Written informed consent was obtained from all included patients before enrollment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2020.08.011.

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