

Long-term outcome and pre-interventional predictors for late intervention
after uterine fibroid embolization

Peer-reviewed author version

D'hoore, Tom; Timmerman, Dirk; LAENEN, Annouschka & Maleux, Geert (2020)
Long-term outcome and pre-interventional predictors for late intervention after
uterine fibroid embolization. In: EUROPEAN JOURNAL OF OBSTETRICS &
GYNECOLOGY AND REPRODUCTIVE BIOLOGY, 247 , p. 149 -155.

DOI: 10.1016/j.ejogrb.2020.02.019

Handle: <http://hdl.handle.net/1942/31348>

Long-term outcome and pre-interventional predictors for late reintervention after uterine fibroid embolization

Tom D'Hoore

Promotor: Prof. Dr. G. Maleux

Co-Promotor: Prof. Dr. D. Timmerman

ABSTRACT

Objectief: Evaluatie van de chirurgische conversie na uteriene fibroomembolisatie (UFE) en identificatie van mogelijk predictoren voor beter klinische resultaten. De mogelijkheid tot zwangerschap na de procedure werd geëvalueerd.

Methodologie: Deze unicentrische retrospectieve cohort studie includeert 190 patiënten die een UFE ondergingen tussen 2001 en 2016. De ernst van symptomen, eventuele heringrepen en post-procedurale fertiliteit werden beoordeeld aan de hand van per post verstuurd vragenlijsten. Patiëntspecifieke gegevens werden uit het patiëntendossier bekomen. De cumulatieve afwezigheid van therapiefalen werd bepaald met Kaplan-Meier analyse. Voor associatie tussen patiëntkarakteristieken en chirurgische reconversie werden Cox Regressie modellen gebruikt.

Resultaten: Opvolging was mogelijk bij 95 van de 190 patiënten met een mediane opvolging van 6.1 jaar. De cumulatieve afwezigheid van therapiefalen is 72.9% na 10 jaar volgens Kaplan-Meier analyse. Symptomatologie daalde met 63.8% en levenskwaliteit steeg 23.3% na UFE. Therapiefalen steeg significante bij toenemend pre-interventioneel uterine volume ($p=0.0003$) of dominant fibroom volume ($p=0.0042$). Negen van de 23 patiënten met kinderwens kregen nog 1 of meerdere kinderen na UFE.

Conclusie: UFE is een goede langetermijnsbehandeling. Toenemend volume uterus of groot dominant fibroom is gecorreleerd met verhoogde chirurgische heringreep. Vrouwen kunnen zwanger worden na UFE in een substantieel aantal gevallen.

Objective: assessment of the long-term freedom from surgical conversion after uterine fibroid embolization (UFE) and to define predictors for better clinical outcome. Additionally, the potential of pregnancy after UFE is assessed.

Methods: This single-center retrospective cohort study includes 190 patients who underwent UFE between 2001 and 2016. Data were obtained by postal questionnaire to define symptom severity, late reintervention rate and to evaluate post procedural fertility. Patient specific characteristics were extracted from the patients' electronic medical records. The cumulative rate of freedom from treatment failure was determined by Kaplan-Meier analysis. Cox regression models were used for univariate analyses of the association between patient preinterventional characteristics and late surgical conversion. Secondary outcome measures were patient specific predictors of treatment failure and evaluation of post-procedural fertility.

Results: Long-term follow-up was available for a median of 6.1 years (range 1.2-15.2 y) in 95 out of 190 patients (50%). Kaplan-Meier analysis of freedom from treatment failure showed a cumulative rate of 72.9% after 10 years and stable until the end of follow-up. A 63.8% reduction in symptoms and a 23.3% increase in quality of life was found. Significant increase of treatment failure was found in patients with increasing pre-interventional uterine volume ($p=0.0003$) or dominant fibroid volume ($p=0.0042$); 9 out of 23 patients (39.1%) with child-bearing wish became pregnant and conceived one or more children after UFE.

Conclusion: UFE is associated with sustained long-term symptom control. Large uteri and large dominant fibroids are correlated with higher late surgical conversion rate. Women can become pregnant and deliver after UFE in a substantial number of cases.

INTRODUCTION

Uterine fibroids are the most common benign tumors of the uterus with a premenopausal cumulative clinically relevant incidence of 50% in black and 35% in white women [1]. The standard treatment for symptomatic fibroids is hysterectomy, but there has been a shift towards less invasive approaches like myomectomy, high intensity focused ultrasound and UFE [2-4]. Mid- and long-term studies evaluating therapy effectiveness after UFE suggest freedom from treatment failure between 70%-90%, based on follow-up times between 1 and 10 years [2,3,5-9]; however, follow-up data longer than 10 years after UFE are scarce as well as preinterventional factors predicting higher risk for treatment failure and late conversion to surgery. Finally, data on fertility after UFE are somewhat contradictory [10-14], and most of the international guidelines consider UFE as a secondary treatment in selected patients with fibroid-related infertility [15-18].

MATERIALS AND METHODS

a. Study design

This is a single-center retrospective study, based on a cohort of 190 patients who underwent UFE between January 2001 and December 2016 in the authors' institution. The study was approved by the institutional review board and patients gave informed consent before completing the questionnaire.

b. study endpoints

The primary endpoint is the analysis of treatment failure (TF) after UFE, defined as the need for a surgical intervention at follow-up. One year follow-up of one year is used. Secondary outcomes are identification of potential patient specific predictors of TF and evaluation of post-embolization fertility.

c. Preinterventional clinical and imaging work-up

Patient characteristics were extracted from the patients' electronic medical files and indications for treatment recorded and categorized into one of four categories: bleeding related symptoms, bulk related symptoms, fertility disorders, or mixed symptoms. Preinterventional imaging characteristics and calculations were performed on magnetic resonance imaging (MRI) in 159 out of 190 patients (87.7%) or color-coded ultrasound in 31 out of 190 patients (16.3%). All imaging studies were available on a Picture Archiving and Communication System (PACS, Agfa, Mortsel, Belgium). 159 patients received an MRI prior to UAE using a torso phased-array coil. The imaging protocol varied over time, but included all following acquisitions:

(1) sagittal and transversal, paratransversal to uterus, paracoronal to uterus T2-weighted turbo spin-echo images (TSE) (repetition time: 4000-5000ms/ echo time: 95ms; matrix: 220-260 x 256; field of view: 240-360 mm x 240-360 mm; section thickness: 4mm)

(2) Paratransversal T1-weighted gradient-echo (GRE) sequences, both unenhanced and contrast-enhanced and fat-saturated (repetition time: 538-1200ms/ echo time: 10-12ms; flip angle: 90°; matrix, 220-260 x 420-512; field of view: 300-420 mm x 300-360 mm; section thickness: 5-6 mm) covering the uterus. Gadolinium-based contrast medium gadoterate meglumine (Dotarem®; Guerbet, Aulnay-sous-Bois, France) with an automatic power injector (flow rate of 2ml/s) was given at a dose of 0.1 mmol/kg of body weight, to all patients as from September 2007. Thirteen scans prior to this date received Gadodiamide (Omniscan®; GE Healthcare) at a dose of 0.1 mmol/kg of body weight.

T2-weighted images were used for evaluating the number of uterine fibroids per patient, which were categorized as singular, 2-5, or more than 5 fibroids. The volume of the dominant fibroid was

calculated by multiplanar segmentation based on MRI data in 159 patients (87.7%) as proposed by Quinn et al. (19). Ultrasound data, prior to the procedure, was used in the remaining 31 patients (16.3%). Volume of the dominant fibroid in these patients was calculated using the formula for an ellipsoid volume ($\frac{4}{3}\pi r_1 r_2 r_3$).

d. Embolization procedure

Patients gave informed consent to the referring gynecologist and attending interventional radiologist before the embolization procedure. The embolization procedure was performed as described earlier (20). Briefly, under spinal anesthesia both uterine arteries were catheterized using a microcatheter through unilateral right femoral access and trisacryl gelatin microspheres (Embosphere 500-700 μm & 700-900 μm , Merit Medical, South Jordan, UT, USA), injected in the uterine arteries by free-flow technique, were used as embolics. Angiographic endpoint was stasis of contrast medium in the uterine artery main branch.

e. Postinterventional follow-up

Patients were followed-up by the attending gynecologist with clinical and ultrasound evaluation at 1 month after embolization and later on if needed. No routine MRI was performed early or late during follow-up.

f. UFS-QOL questionnaire mail survey

A questionnaire including 36 questions (Table I) and based upon the UFS-QOL questionnaire as previously described by Spies et al. [21] was used. The questionnaire and the informed consent for the study was mailed to each patient in January – February 2017. Patients were invited to read and, if agreed, sign the informed consent, and complete the questionnaire and return them by pre-paid addressed envelopes to the investigators. Pre-intervention data were gathered in the first section of the questionnaire. The second section included questions, focused on fibroid related physical and psychological symptoms, in the period after the procedure. The focus in the third section was on fertility and treatment failure. Patients were asked to score their symptoms on a 5-point Likert scale (1 = no impact, 5 = very much impacted). The formula suggested by Spies et al. [21] was used to calculate a symptom severity score, with higher score values indicating a higher symptom severity and lower scores indicate lower symptom severity. An inverted formula was used to calculate a quality of life score and included parameters for sexual dysfunction, limitations in social life and depressed mood. Higher scores indicate better quality of life.

g. Statistical analysis

A statistical comparison of anonymized patient characteristics between respondents and non-respondents to the mailed questionnaire, was made using SAS 9.4 statistical software (Cary, NY, USA). The comparison was performed using Chi-square test for categorical variables and Mann-Whitney U test for continuous variables. A p-value of less than 0.05 was considered significant.

Cox regression models were used for univariate analyses of the association between patient preinterventional characteristics and need for postinterventional surgical conversion.

RESULTS

Patients' characteristics

There were no significant differences in preinterventional characteristics between group 1 and group 2 (Table II). One patient died of non-related causes in the follow-up period; 189 questionnaires were sent out; 23 questionnaires never reached their destination because of patients' unknown address

changes and 10 questionnaires were incompletely filled in and returned. A total of 95 (50%) completed questionnaires were sent back and included in the study (Fig. 1).

Quality of Life Questionnaire

Time interval between intervention and follow-up ranges from 1.2 to 15.2 years with a mean follow-up period of 6.1 years. Improvement of clinical symptoms was achieved in 72 out of 95 patients (75.8%), based on the non-validated questionnaire. The mean pre-procedural symptom severity score was 47.1 [QR; 35.00-62.50] and 17,06 [QR; 7.5-22.5] after embolization which is a reduction in symptoms of 63.83% ($p < 0.0001$). The mean Quality of Life (QOL) score before intervention was 73.05 [QR; 58.33-92.71] and 89.54 [QR; 83.33-100] after embolization, which is an improvement of 23.3% ($p < 0.0001$).

18 (18.9%) patients underwent a second intervention, defined as treatment failure, at a median of 2,3 years (QR; 1.0 – 3.5 y) after UFE. 10 patients underwent hysterectomy as second intervention. Seven patients had myomectomy and one underwent repeat UFE. Five patients reported no improvement of clinical symptoms, but refused further therapy.

Follow-up

Kaplan-Meier analysis of freedom from TF showed a cumulative rate of 82.18% after 5 years, 72.88% after 10 years and stable until the end of follow-up (Fig. 2, Table III).

Various parameters including age, location of dominant fibroid, number of fibroids or preprocedural symptoms could not reveal a relation with late outcome after UFE (Table IV). Larger total uterine volume ($p < 0.0001$) and volume of the dominant fibroid ($p = 0.0003$) were identified as predictors for late failure rate after UFE.

The risk of TF was five times higher in women with a large uterus (>500ml) compared to women with a uterus < 200ml and 3 times higher compared to women with uterine volumes between 200 and 500ml (fig 3). A dominant fibroid volume of >200ml has a significant higher risk of TF, as demonstrated in Kaplan-Meier analysis (fig 4). Women with a large fibroid (>500ml) had 8.8 times higher risk compared to women with smaller fibroids (<200ml).

Fertility after UFE

23 patients (mean age 32.6 years (ranging from 22 to 41y)) in our cohort expressed their desire to become pregnant after the procedure; 9 out of 23 (39.1%) patients became pregnant and had one or more children after the full term pregnancy. Two patients had an ectopic pregnancy and twelve patients did not become pregnant anymore. Five patients underwent the UFE primarily because of infertility. Four of them mentioned this as their only complaint. One patient also had bleeding related symptoms. Three (60%) women had successful pregnancies after the embolization in this group.

Last, 5 out of 9 patients with a term pregnancy delivered through a Caesarean section, 2 by vaginal delivery and mode of delivery was unknown in the remaining 2 patients.

DISCUSSION

This study demonstrates a significant drop in symptom severity scores from preprocedure (47.2) to late after embolization (17.1) over a median follow-up of 6.1 years. These results are in line with reported symptom improvement, measured earlier after embolotherapy. Scheurig-Muenkler et al. (2) found symptom severity scores after 5.7 years: 46.8 (34-62) to 3.1 (0-15.6). The FIBROID registry

revealed nearly identical improvements three years after UFE, demonstrating a drop in score from 58.6 before UFE to 16.5 three years after UFE [22] and Popovic et al. [23] revealed continued symptom control for UFE with a median of 7 years of follow-up in 33 patients. The present study suggests a sustained symptom control with good quality of life long after the UFE, considering UFE as an effective and durable treatment option for patients with symptomatic uterine fibroids. This consideration might be powered by the fact that in this study less than 20% of patients needed a late second intervention after UFE for failed treatment. These results are in accordance or even slightly better than published failure rates and late reinterventions after UFE: Scheurig-Muenkler et al. reported a failure rate of 23.3% after median 5.7 years of follow-up (2) and Dutton et al. found a 23% risk of requiring further treatment for fibroids after UFE, with a median of 4.6 years of follow-up [24].

The secondary objective of the present study is the analysis of potential preinterventional predictors for late treatment failure. Both baseline total uterine volume and dominant fibroid volume were identified as clear predictors for late reintervention. Women with baseline uterine volumes greater than 500 ml were five times more likely to undergo a reintervention compared to those with volumes less than 200 ml, or 3.5 times more likely, compared to patients with a uterine volume between 200 – 500 ml. Additionally, patients with a baseline dominant fibroid volume less than 200 ml were up to nine times less likely to undergo a subsequent intervention, compared to women with fibroids of less than 500 ml, or more than four times less likely than patients with fibroids between 200 and 500 ml. These data are in analogy with Spies et al. [25] and Marret et al. [26] who also reported fibroid volume as a predictor for treatment failure. Additionally, the FIBROID registry found that increasing fibroid size is a predictor for poorer symptom score outcome at 36 months compared with score at baseline [22]. Other authors failed to identify uterine volume or dominant fibroid volume as a preinterventional predictor for treatment failure [27-29]. Potential factors associated with these contradictory results might be a difference in range of uterine volumes (6), making statistical analysis less accurate; or the methodology of volume calculation. In the present study, MRI-based parallel planimetric measurements were used instead of the ellipsoid formula [19], which are used in earlier reports [30]. Ellipsoid formula is less accurate than MRI-based planimetric calculations and is subject to more interobserver variability [31]. Last, we could not find preinterventional demographic characteristics as risk factors for late reintervention, which is in contrast to Tropeano et al. [32] and Scheurig-Muenkler et al. [33] who identified the risk of treatment failure to be twice as high for patients < 40 years of age compared to patients above the age of 45 years.

Although several studies reported term pregnancies after UFE [9,10-12,14,34-36], early guidelines considered a potential patient's childbearing wish as a contraindication for UFE [32]. In the present report, nearly 40% of patients (n=9/23) who expressed their wish for a pregnancy after UFE, had a term pregnancy; another 2 patients had ectopic pregnancy and the remaining 12 patients did not become pregnant. These findings are in line with earlier reports dealing with pregnancy after UFE: Walker et al. reported 10 pregnancies in 24 women (40%) actively trying to become pregnant after UFE [9]. Finally, this study confirms the high rate of Caesarean sections after UFE as already suggested by Torre et al [35]: in the present study more than 50% of patients delivered through a Caesarean section after UFE.

This report has also some limitations. First, this is a retrospective study based on a questionnaire, including baseline demographic data, which were sent to the patients long after the UFE-procedure. Additionally, the questionnaires were administered over varying times after the embolization procedure and potential bias may exist as patients might minimize initial symptoms in this remote recall situation, resulting in lower apparent therapeutic benefit of UFE [37]. Second, only 50% of treated patients completed and sent back the questionnaire. However, statistical reports dealing with analysis of questionnaires can be considered as robust if 50% of patients completed all study documents [38]. In addition, no significant difference was found in between preinterventional data of respondents and non-respondents.

In conclusion, this report demonstrates a good and durable long-term outcome of UFE with regard to fibroid-related symptom control. Larger size uterus and dominant fibroid are associated with a higher

failure rate and a need for late, second uterine reintervention. Last, potential future pregnancy should not be considered anymore as a contraindication for after UFE.

CONCLUSION

In this long term follow-up study we established UAE as a good and durable long-term treatment option for symptomatic fibroids. Large uteri and large dominant fibroids are correlated with higher failure rates and can possibly be used as a parameter for patient selection in order to increase treatment success. Fertility outcomes from this study demonstrate the potential for women to become pregnant and deliver after UFE.

REFERENCES

1. D. D. Baird, D. B. Dunson, M. C. Hill, D. Cousins and J. M. Schectman, High cumulative incidence of uterine leiomyoma in black and white women: Ultrasound evidence. *Am J Obstet Gynecol* 2003; 188(1):100-7.
2. C. Scheurig-Muenkler, C. Koesters, M. J. Powerski, C. Grieser, V. Froeling and T. J. Kroencke. Clinical Long-term Outcome after Uterine Artery Embolization: Sustained Symptom Control and Improvement of Quality of Life. *J Vasc Interv Radiol* 2013; 24(6):765-71
3. B. Poulsen, T. Munk and P. Ravn. Long-term follow up after uterine artery embolization for symptomatic uterine leiomyomas. *Acta Obstet Gynecol Scand.* 2011; 90(11):1281-3.
4. Sandberg E, Tummers F, Cohen S, van den Haak L, Dekkers O, Jansen F. Reintervention risk and quality of life outcomes after uterine-sparing interventions for fibroids : a systematic review and meta-analysis. *Fertil Steril* 2018; 109:698-707.
5. S. Duvnjak, P. Ravn, A. Green and P. E. Andersen. Clinical Long-Term Outcome and Reinterventional Rate After Uterine Fibroid Embolization with Nonspherical Versus Spherical Polyvinyl Alcohol Particles. *Cardiovasc Intervent Radiol* 2016; 39(2):204-9.
6. H. Hamoda, L. Pepas, F. Tasker, J. Reidy and Y. Khalaf. Intermediate and long-term outcomes following uterine artery fibroid embolization. *Eur J Obstet Gynecol Reprod Biol* 2015; 191:33-8.
7. P. N. M. Lohle, M. J. Voogt, J. De Vries, A. J. Smeets, H. A. M. Vervest, L. E. H. Lampmann and P. F. Boekkooi. Long-term Outcome of Uterine Artery Embolization for Symptomatic Uterine Leiomyomas. *J Vasc Interv Radiol* 2008; 19(3):319-26.
8. Duvnjak S, Ravn P, Green A, Andersen P. Clinical longterm outcome and reintervention rate after uterine fibroid embolization with nonspherical versus spherical polyvinyl alcohol particles. *Cardiovasc Intervent Radiol* 2016; 39:204-9.
9. Walker W, Barton-Smith P. Long-term follow-up of uterine artery embolization – an alternative in the treatment of fibroids. *BJOG* 2006; 113:464-8.
10. Mara M, Maskova J, Fucikova Z, Kuzel D, Belsan T, Sosna O. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. *Cardiovasc Intervent Radiol* 2008; 31:73-5.
11. Laurent A, Pelage J, Wassef M, Martal J. Fertility after bilateral uterine artery embolization in a sheep model. *Fertil Steril* 2008; 89:1371-83.
12. Goldberg J, Pereira L, Berghella V. Pregnancy after uterine artery embolization. *Obstet Gynecol* 2002; 100:869-72.
13. Smith W, Upton E, Shuster E, Klein A, Schwartz M. Patient satisfaction and disease specific quality of life after uteirne fibroid embolization. *Am J Obstet Gynecol* 2004; 190:1697-703.

14. Pisco J, Duarte M, Bilhim T, Branco J, Cirurgiao F, Forjaz M, Fernandes L, Pereira J, Costa N, Pisco J, Oliveira A. Spontaneous pregnancy with a life birth after conventional and partial uterine fibroid embolization. *Radiology* 2017; 285:302-10.
15. D. M. Hovsepian, G. P. Siskin, J. Bonn, J. F. Cardella, T. W. Clark, L. E. Lampmann, D. L. Miller, R. A. Omary, J.-P. Pelage, D. Rajan, M. S. Shwartzberg, R. B. Towbin, W. J. Walker and D. Sacks. Quality Improvement Guidelines for Uterine Artery Embolisation for Symptomatic Leiomyomata. *Cardiovasc Intervent Radiol* 2004; 27(4):307-13.
16. Committee on Gynecologic Practice, American College of Obstetricians and Gynecologists. ACOG committee opinion: uterine fibroid embolization. *Obstet Gynecol* 2004; 103:403-404.
17. The Royal College of Obstetricians and Gynecologists, Clinical recommendations on the use of uterine artery embolization in the management of fibroids, Third edition.
18. J. H. Ravina, N. Ciraru-Vigneron, J. M. Bouret, D. Herbreteau, E. Houdart, A. Aymard and J. J. Merland. Arterial embolisation to treat uterine myomata. *Lancet* 1995; 346(8976):671-2.
19. S. D. Quinn, J. Vedelago, E. Kashef, W. Gedroyc and L. Regan. Measurement of uterine fibroid volume: A comparative accuracy and validation of methods study. *Eur J Obstet Gynecol Reprod Biol* 2013; 171(1):161-5.
20. Maleux G, Michielsen K, Timmerman D, Poppe W, Heye S, Vaninbrouckx J, Bosmans H. 2D versus 3D roadmap for uterine artery embolization : impact on several angiographic parameters. *Acta Radiol* 2014; 55:62-70.
21. J. B. Spies, K. Coyne, N. Guaou Guaou, D. Boyle, K. Skyrnarz-Murphy and S. M. Gonzalves. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet Gynecol* 2002; 99(2):290-300
22. Goodwin S, Spies J, Worthington-Kirsch R, Peterson E, Pron G et al. Uterine artery embolization for treatment of leiomyomata : long-term outcomes from the FIBROID registry. *Obstet Gynecol* 2008; 111:22-33.
23. M. Popovic, D. Berzacy, S. Puchner, A. Zadina, J. Lammer and R. A. Bucek. Long-Term quality of life assessment among patients undergoing uterine fibroid embolization. *Am J Roentgenol* 2009; 193(1):267-71.
24. Dutton S, Hirst K, McPherson K, Nicholson T, Maresh M. A UK multicentre retrospective cohort study comparing hysterectomy and uterine fibroid embolization for the treatment of symptomatic uterine fibroids (HOPEFUL study) : main results on medium-term safety and efficacy. *BJOG* 2007; 114:1340-1351.
25. J. B. Spies, J. Bruno, F. Czeyda-Pommersheim, S. T. Magee, S. A. Ascher and R. C. Jha. Long-Term Outcome of Uterine Artery Embolization of Leiomyomata. *Obstet Gynecol* 2005; 105(5 pt1):933-9.
26. H. Marret, J. P. Cottier, A. M. Alonso, B. Giraudeau, G. Body and D. Herbreteau. Predictive factors for fibroids recurrence after uterine artery embolization. *BJOG* 2005; 112(4):461-5.
27. Gabriel-Cox K, Jacobson G, Armstrong M, Hung Y, Learman L. Predictors of hysterectomy after uterine artery embolization for leiomyoma. *Am J Obstet Gynecol* 2007; 196: 588 e1-6.
28. Isonishi S, Coleman R, Hiramama M et al. Analysis of prognostic factors for patients with leiomyoma treated with uterine arterial embolization. *Am J Obstet Gynecol* 2008; 198:271-276.
29. Prollius A, de Vries C, Loggenberg E, du Plessis A, Nel M, Wessels P. Uterine artery embolization for symptomatic fibroids: the effect of the large uterus on outcome. *BJOG* 2004; 111:239-242.
30. Yoon J, Han K, Kim M, Kim G, Kwon J, Won J, Lee D. Five-year clinical outcomes of uterine artery embolization for symptomatic leiomyomas: An analysis of risk factors for reintervention. *Eur J Radiol* 2018; 109:83-87.
31. M. C. Fonseca, R. Castro, M. Machado, T. Conte and M. J. Girao. Uterine Artery Embolization and Surgical Methods for the Treatment of Symptomatic Uterine Leiomyomas: A Systemic Review and Meta-analysis Followed by Indirect Treatment Comparison. *Clin Ther* 2017; 39(7):1438-55.

32. G. Tropeano, C. Di Stasi, S. Amoroso, G. Vizzielli, F. Mascilini and G. Scambia. Incidence and risk factors for clinical failure of uterine leiomyoma embolization. *Obstet Gynecol* 2012; 120(2):269-76.
33. C. Scheurig-Muenkler, C. Koesters, C. Grieser, B. Hamm and T. J. Kroencke. Treatment failure after uterine artery embolization: Prospective cohort study with multifactorial analysis of possible predictors of long-term outcome. *Eur J Radiol* 2012; 81(5):727-31.
34. B. McLucas, S. Goodwin, L. Adler, A. Rappaport, R. Reed and R. Perrella. Pregnancy following uterine fibroid embolization. *Int J Gynaecol Obstet* 2001; 74(1):1-7.
35. Torre A, Fauconnier A, Kahn V, Limot O, Bussierres L, Pelage J. Fertility after uterine artery embolization for symptomatic multiple fibroids with no other fertility factors. *Eur Radiol* 2017; 27:2850-2859.
36. W. J. Walker and S. J. McDowell. Pregnancy after uterine artery embolization for leiomyomata: A series of 56 completed pregnancies. *Am J Obstet Gynaecol* 2006; 195(5):1266-71.
37. R. A. Bucek, S. Puchner and J. Lammer. Mid- and long-term quality-of-life assessment in patients undergoing uterine fibroid embolization. *Am J Roengenol* 2006; 186(3):877-82.
38. J. S. Armstrong and T. S. Overton. Estimating Nonresponse Bias in Mail Surveys. *J Marketing Res* 1977; 14(3):396-402.

Table I: Patient's questionnaire

PART I and II included the same question, respectively focus on the period before the embolization and the period after embolization:

| | Not at all (1) | A little (2) | Some (3) | Quite a lot (4) | Very much (5) |
|--|-------------------|-----------------|-------------|--------------------|------------------|
| Did you have heavy bleeding during your menstrual periods? | | | | | |
| Did you have blood clots during your menstrual periods? | | | | | |
| Did you have bleeding at unpredictable times, in between your menstrual periods? | | | | | |
| Did you have menstrual periods with variable duration? | | | | | |
| Was your menstrual cycle variable in length? | | | | | |
| Did you have a feeling of pressure in your lower abdomen? | | | | | |
| Did you have pain in your lower abdomen or back? | | | | | |
| Did you need to urinate frequently during the day? | | | | | |
| Did you need to urinate frequently at night? | | | | | |
| Did you feel tired? | | | | | |
| Did you experience pain when having sex? | | | | | |
| Did you avoid sexual activity? | | | | | |
| Did you avoid certain activities due to anxiety about bleeding or pain? | | | | | |
| Did you feel less productive? | | | | | |
| Was it difficult to carry out your everyday activities? | | | | | |
| Did you feel unhappy or low in mood? | | | | | |

PART III focused on treatment failure and fertility:

| | | | |
|--|----------------------|--|--------------------------------|
| After embolization the symptoms were not adequately controlled or the symptoms had become worse and I had an additional procedure as a result: | | | |
| No | Further embolization | Surgical removal of fibroids without removing the uterus | Surgical removal of the uterus |

| | | |
|---|------------------|---|
| About your menstrual periods: | | |
| I no longer have monthly menstrual periods (Menopause). | I am on the pill | I still have monthly menstrual periods. |

| | | |
|---|-----|----|
| Did you, or do you still wish to become pregnant after the procedure? | Yes | No |
| Have you been pregnant successfully since the procedure? | Yes | No |

Table II: Demographic characteristics. Baseline characteristics of group 1: ‘respondents’ (=patients with completed questionnaire) and group 2: ‘non-respondents’ (=patients not sending back or sending back an incompletely filled in questionnaire)

| Variable (median – [range]) | Group 1 (n=95) | Group 2 (n=94) | P-value |
|------------------------------------|-----------------------|-----------------------|----------------|
| Follow-up time (y) | 6.1 [1.2 – 15.2] | 6.1 [1.0 – 16] | 0.791 |
| Age at embolization (y) | 42 [22 - 60] | 41 [26 – 53] | 0.600 |
| Uterine volume (ml) | 372 [44.9 – 2357] | 351 [65.4 – 3402] | 0.584 |
| Dominant fibroid volume (ml) | 186 [2 – 1136] | 177.3 [3.6 – 1283.3] | 0.455 |
| Location Dominant fibroid | | | 0.267 |
| Intramural | 64/95(67.37%) | 56/95 (58.95%) | |
| Submucosal | 16/95 (16.84%) | 15/95 (15.79%) | |
| Subserosal | 15/95 (15.79%) | 24/95(25.26%) | |
| Number of fibroids | | | 0.440 |
| 1 | 50/95 (52.63%) | 39/95 (41.05%) | |
| 2 | 7/95 (7.37%) | 13/95 (13.68%) | |
| 3 | 11/95 (11.58%) | 9/95 (9.47%) | |
| 4 | 6/95 (6.32%) | 5/95 (5.26%) | |
| 5 | 3/95 (3.16%) | 5/95 (5.26%) | |
| >5 | 18/95 (18.95%) | 24/95 (25.26%) | |
| Symptom distribution | | | 0.278 |
| Bleeding | 38 (40%) | 51 (54.26%) | |
| Bulk | 9 (9.47%) | 10 (10.64%) | |
| Fertility | 5 (5.26%) | 4 (4.26%) | |
| Mixed | 43 (45.26%) | 30 (31.91%) | |

Table III - Kaplan-Meier estimates for cumulative rate of freedom from TF (second intervention)

| Months | % without re-intervention (95% CI) |
|---------------|---|
| 12 | 94.74 (87.82 – 97.77) |
| 24 | 90.41 (82.38 – 94.89) |
| 36 | 86.64 (77.61 – 92.21) |
| 48 | 83.97 (74.33 – 90.22) |
| 60 | 82.18 (71.93 – 88.97) |
| 120 | 72.88 (57.63 – 83.39) |

Table IV: Results of Cox Proportional Hazards Regression. Univariate analyses of the association between patient characteristics and reintervention. A significant p-value was found for uterus and dominant fibroid volume at baseline.

| Variable | Hazard Ratio (95% CI) | P-value |
|-------------------------------------|------------------------------|----------------|
| Age | 0.974 (0.913 - 1.038) | 0.4131 |
| Uterus volume at baseline (global) | 1.002 (1.001 - 1.003) | <.0001 |
| Uterus volume at baseline(category) | | 0.0162 |
| 200-500ml versus <200ml | 1.477 (0.286 - 7.618) | 0.6412 |
| >500ml versus <200ml | 5.259 (1.160 - 23.832) | 0.0313 |
| >500ml versus 200-500ml | 3.560 (1.227 - 10.331) | 0.0195 |
| Location dominant myoma (global) | | 0.6699 |
| Number of fibroids | 0.991 (0.777 - 1.264) | 0.9442 |
| Dominant fibroid volume (global) | 1.003 (1.001 - 1.004) | 0.0003 |
| Dominant fibroid volume (category) | | 0.0042 |
| 200-500ml versus <200ml | 4.445 (1.612 - 12.256) | 0.0039 |
| >500ml versus <200ml | 8.803 (1.736 - 44.630) | 0.0086 |
| >500ml versus 200-500ml | 1.981 (1.169 - 7.946) | 0.3840 |
| Symptom category (global) | | 0.6066 |

FIGURES

Fig. 1: Flow chart of questionnaire survey (33 incompletely filled in questionnaires)

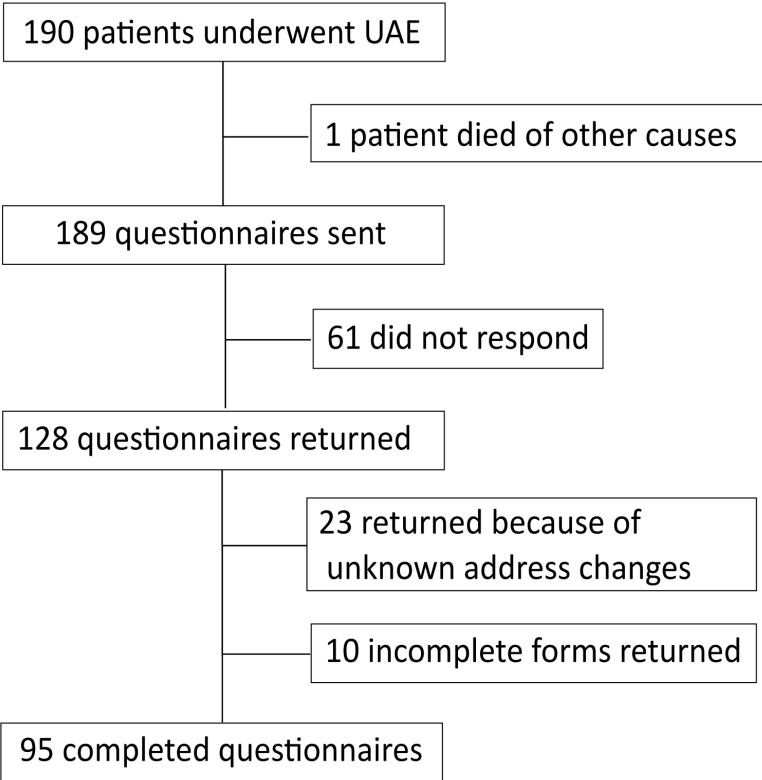
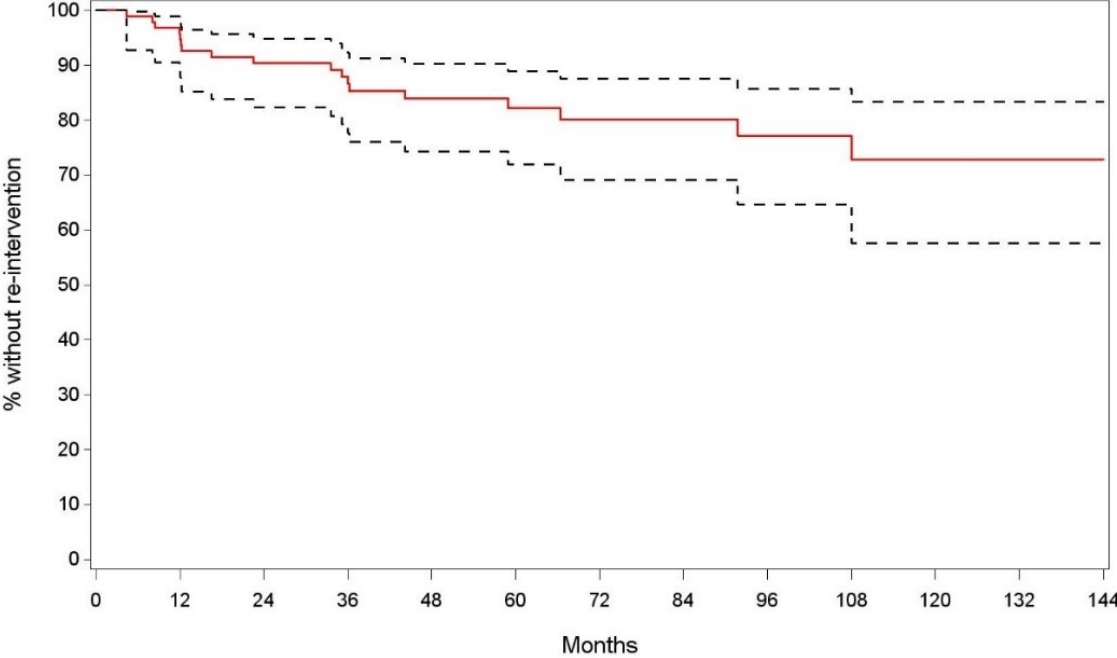
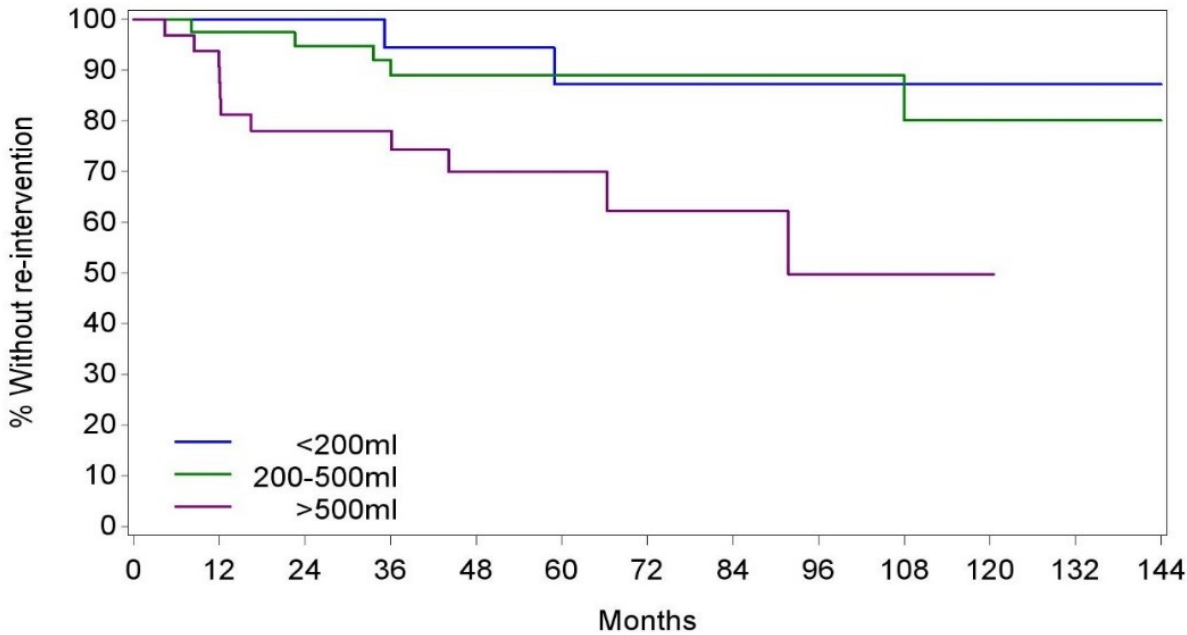


Fig. 2: Kaplan-Meier analysis of freedom from TF (second intervention) for all patients included for follow-up (n= 95). Number of patients at risk each year. The cumulative rate of freedom from TF is 72,9% after 120 months.



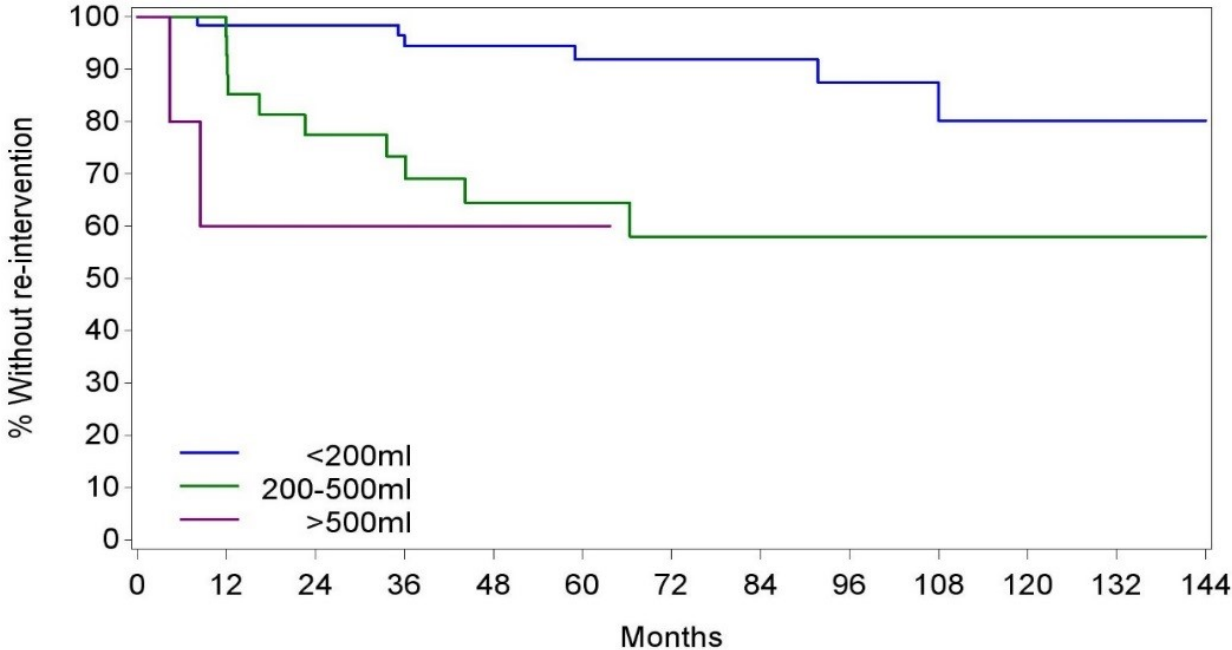
| Number at risk | | | | | | | | | | | | |
|----------------|----|----|----|----|----|----|----|----|----|----|----|---|
| 95 | 91 | 79 | 68 | 57 | 45 | 35 | 30 | 24 | 18 | 13 | 11 | 5 |

Fig. 3: Kaplan-Meier analysis of freedom from TF (treatment failure) for categoric baseline uterine volumes.



| Number at risk | | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 | 132 | 144 |
|----------------|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|
| <200ml | 24 | 24 | 24 | 21 | 17 | 16 | 11 | 9 | 9 | 7 | 5 | 5 | 4 | 3 |
| 200-500ml | 39 | 38 | 36 | 30 | 26 | 23 | 19 | 15 | 13 | 10 | 7 | 7 | 7 | 2 |
| >500ml | 32 | 29 | 22 | 21 | 15 | 11 | 7 | 6 | 4 | 3 | 1 | 0 | 0 | 0 |

Fig. 4: Kaplan-Meier analysis of freedom from TF (treatment failure) for categoric baseline dominant fibroid volumes.



| Number at risk | | | | | | | | | | | | | |
|----------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|
| | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 | 132 | 144 |
| <200ml | 63 | 62 | 57 | 49 | 41 | 33 | 26 | 23 | 18 | 12 | 10 | 9 | 4 |
| 200-500ml | 27 | 26 | 20 | 17 | 14 | 11 | 9 | 7 | 6 | 6 | 3 | 2 | 1 |
| >500ml | 5 | 3 | 2 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |