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CLINICAL ARTICLE

Interim analysis of a randomized controlled trial comparing laparoscopic radiofrequency volumetric thermal ablation of uterine fibroids with laparoscopic myomectomy

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ABSTRACT

Objective: To compare 24-month patient-reported outcomes following laparoscopic radiofrequency volumetric thermal ablation (RFVTA) and laparoscopic myomectomy in patients with uterine fibroids. *Method:* An interim analysis of 24-month follow-up data from a randomized controlled trial was performed at Tübingen University Women's Hospital between November 1, 2012 and May 30, 2015. Premenopausal patients, at least 18 years of age, who were menstruating, were randomly assigned to be treated for symptomatic uterine fibroids with either RFVTA or laparoscopic myomectomy. The outcomes included in the present per-protocol analysis were patients' responses to validated questionnaires and long-term safety. *Results:* The study enrolled 51 patients; 21 and 22 patients in the RFVTA and laparoscopic myomectomy groups, respectively, completed 24 months of follow-up. Improvements in the severity of symptoms from baseline were reported by participants in both the RFVTA ($P < 0.001$) and laparoscopic myomectomy groups ($P = 0.001$). A significant improvement in health-related quality of life was observed in the laparoscopic myomectomy group ($P = 0.040$); a non-significant improvement was recorded in the RFVTA group ($P = 0.083$). A trocar-site hematoma occurred in one patient in the laparoscopic myomectomy group. Further surgical interventions were recorded in three patients in the RFVTA group but these were unrelated to fibroid symptoms. *Conclusions:* These 24-month data suggest equivalence in safety and patient-reported efficacy of RFVTA and laparoscopic myomectomy.

ClinicalTrials.gov: NCT01750008

1. Introduction

Targeted radiofrequency ablation (RFA) of tissue for palliative and therapeutic applications has been well documented in the literature for the treatment of cardiac arrhythmias [1], neurological and spinal disorders [2,3], and cancers of the liver [4], kidney [5], prostate [6], breast [7], lung [8], and skin [9]. However, to date only one RFA system, employing radiofrequency volumetric thermal ablation (RFVTA) has received FDA approval for the treatment of symptomatic uterine fibroids in the United States (Acessa; Halt Medical, Inc, Brentwood, CA, USA). RFVTA has also been approved for use in Europe.

Uterine fibroids are the most ubiquitous benign uterine masses in reproductive-aged women, occurring in up to 80% of this group; of these individuals, 25%–30% experience related bleeding, pain, and bulk symptoms [10,11]. Symptomatic fibroids are a significant healthcare and economic burden worldwide, significantly affecting patients' quality of life. Treatment success is usually evaluated in terms of improvements in quality of life. Traditionally, hysterectomy was the approach employed in the treatment of fibroids; however, patients have increasingly sought minimally invasive, uterine-sparing therapies that also preserve reproduction function. Consequently, excisional laparoscopic myomectomy is considered the gold standard by most clinicians [12]. Similarly, RFVTA is a minimally invasive and uterine-sparing procedure. It is guided intraoperatively using laparoscopic ultrasound, which has been demonstrated to detect more uterine fibroids (regardless of their location and size) than either transvaginal ultrasound or contrast-enhanced magnetic resonance imaging [13]. RFVTA delivers well-controlled thermal treatment zones without affecting surrounding tissues or organs and it can be applied to large fibroids, multiple fibroids, and deep intramural fibroids [14,15].

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Patient responses to various validated questionnaires are useful in gauging the success of any treatment for uterine fibroids. The Uterine Fibroid Symptom and Quality of Life (UFS–QOL) questionnaire provides valid, and highly responsive and reliable measures for assessing the symptoms and health-related quality of life in patients with symptomatic uterine fibroids; additionally, it can be used to compare outcomes of fibroid therapies [16,17]. Similarly, the EuroQoL (EQ-5D) health-state survey is a validated, multi-attribute health-state classification system that indicates the burden of illness in terms of mobility, self-care, ability to complete normal activities, pain/discomfort, and anxiety or depression [18]. The menstrual impact questionnaire (MIQ) is especially useful for gauging the burden of menstrual bleeding a patient is experiencing at the time of questioning [19].

The aim of the present interim analysis was to analyze the 24-month efficacy and safety outcomes from an ongoing randomized controlled trial of laparoscopic ultrasound-guided RFVTA and laparoscopic ultrasound-guided myomectomy (ClinicalTrials.gov: NCT01750008) [15,20] for the treatment of symptomatic uterine fibroids.

2. Materials and methods

An interim analysis was performed on data from an ongoing randomized, prospective, single-center, longitudinal trial of laparoscopic myomectomy and RFVTA that began November 1, 2012. Premenopausal patients who were menstruating, aged at least 18 years, with symptomatic fibroids, who desired uterine conservation, and were indicated for surgical intervention for their fibroid symptoms were referred to Tübingen University Hospital, Germany, for study enrollment between November 1, 2012 and June 30, 2013. Eligible patients had a uterine size of no more than 16 gestational weeks, no individual fibroid with a largest dimension of greater than 10 cm on transvaginal ultrasound, and a normal Papanicolaou test. Exclusion criteria included being at risk for, or known to have, significant intra-abdominal adhesions that would require extensive dissection to mobilize and view all surfaces of the uterus; pregnancy or lactation; having received any depot gonadotropin-releasing hormone agonist within the 3 months prior to the procedure; the presence of an implanted intrauterine or fallopian tube device at any time up to 10 days before treatment; known or suspected endometriosis or adenomyosis; pelvic inflammatory disease; gynecologic malignancy or pre-malignancy in the 5 years before enrollment; history of pelvic radiation; the presence of a non-uterine pelvic mass larger than 3 cm at its greatest diameter or the presence of a cervical fibroid; one or more intracavitary (Type 0 or Type 0/1) fibroids that would be better treated by hysteroscopic means; and not willing to be randomized for treatment. The study protocol required that patients provide written informed consent after agreeing that they understood the study purpose, the associated testing, procedures, and follow-up assessments, as well as the potential risks and benefits of participation. The Clinical Ethics Committee of Tübingen University Hospital in Tübingen, Germany approved the study, and all enrollees were treated at Tübingen University Hospital. Data were collected and monitored (CenTrial GmbH, Tübingen, Germany) in Tübingen and were analyzed by an independent biostatistics firm in the United States (Innovative Analytics Inc, Kalamazoo, Michigan USA).

Patients were randomly allocated in a 1:1 ratio to receive either laparoscopic myomectomy or RFVTA. Randomization occurred as an intraoperative step after the surgeon mapped the patient's uterus for the location, number, and types of fibroids using laparoscopic ultrasound. The use of laparoscopic ultrasound provided additional imaging information to the surgeon regarding the patient's fibroids, regardless of their treatment assignment. After mapping, the operating room staff drew an envelope containing the patient's computer-generated treatment assignment. Assignments were generated by an independent biostatistician in blocks of six or four. The surgeon and patient were masked to treatment assignment prior to the beginning of surgery.

Patients assigned to undergo myomectomy were placed in the lithotomy position and underwent standard laparoscopic myomectomy [15]. If deep intramural fibroids or transmural fibroids not encroaching on the serosal borders were encountered, two-layer suturing was used. Although the excision of all fibroids was allowed per protocol, intramural fibroids 1.0–1.5 cm in diameter were not excised owing to the clinical standard of care at the study institution.

The RFVTA treatment procedure and the methods for pretreatment tissue sampling for histopathology have been described in detail previously [15,20–23]. RFVTA treatment involved the use of a monopolar radiofrequency generator, a percutaneously placed handpiece incorporating an electrode at its distal tip with a deployable array, two large dispersive electrode pads, extension cables, and an activating foot pedal. Current was delivered to the small electrode tip and array; this facilitated the localization of ablative treatment to the fibroid tissue. The current was removed via large dispersive electrode pads that were placed on each patient's thighs above the patella. The electrical current resulted in the oscillation of intracellular ions, generating resistive or frictional heating. The heat spread by conduction, decreasing rapidly with increasing distance from the electrode ($1/d^4$) (Fig. 1A, B, and C). The current continued through the body to the dispersive electrode pads, where it returned to the source. The ablated tissue underwent coagulative necrosis and was naturally reabsorbed by the surrounding myometrium.

The target ablation temperature was 100 °C and the required time at the target temperature was a function of the length of array deployment. An algorithm was used to define the deployment and time at 100 °C. Following the completion of the recommended ablation time the surgeon depressed the foot pedal, ending the ablation. The array was then withdrawn into the handpiece shaft, the probe was switched from ablation to coagulation mode, and the track was coagulated during handpiece withdrawal. Hemostasis was confirmed through laparoscopic viewing. Following the ablation of all fibroids, the pelvis was irrigated and inspected, the port sites were closed using intracutaneous sutures, and patients were discharged from the clinic on the same day.

The primary outcome of the ongoing 5-year randomized controlled trial is the length of hospital stay. The secondary outcomes are patients' responses to questionnaires. The analyses of patient hospitalization and perioperative outcomes have been described previously [15].

The present interim analysis of the study reports 24-month postoperative qualitative outcomes in terms of participants' responses to questionnaires (UFS–QOL, EQ-5D, overall treatment effect survey, and the MIQ [16–19]), re-interventions for fibroid symptoms, and pregnancy outcomes. According to the study method, the participants will be followed for a total of 5 years.

The calculation of the sample size has been described in detail previously [15] and was based on hospitalization times for patients in each group. Briefly, the null hypothesis was that the duration of hospitalization for patients who underwent the RFVTA procedure would be more than 10% longer than that experienced by patients who underwent laparoscopic myomectomy. The alternative hypothesis was that this would not be the case, resulting in a one-sided non-inferiority test of RFVTA in comparison with laparoscopic myomectomy, with an alpha level of 0.025. Based on procedures in the USA (unpublished data), the null hypothesis would be rejected if the mean length of hospital stay for patients undergoing RFVTA was 7 ± 4 hours. The mean length of hospital stay for women undergoing laparoscopic myomectomy has been demonstrated to be approximately 15 ± 16 hours [24]. The pooled standard deviation of the difference in length of hospital stay between these two procedures is 11.7 hours, which is the square root of the mean of the estimated variances of the two procedures. The power yielded under these assumptions is 0.80, resulting in a necessary sample size of 50 participants (25 in each group).