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UTERINE FIBROIDS AND ENDOMETRIAL LESIONS (T. TULANDI, SECTION EDITOR)

A Novel Approach for Treatment of Uterine Fibroids: Stereotactic Radiosurgery as a Proposed Treatment Modality

Camran Nezhat[1,2,3] • Nataliya Vang[1,2] • Mailinh Vu[1,2] • Jessica Grossman[4] • Jayne Skinner[1] • Kelly Robinson[1] • Komal Saini[1] • Anuj Vaid[1] • Laura Maule[1] • John R. Adler[2] • Joanne W. Jang[5] • Iris C. Gibbs[2]

Abstract

Purpose of Review Minimally invasive therapeutic interventions and the field of stereotactic radiosurgery have advanced enormously in recent years. We briefly review the field of stereotactic radiosurgery and propose its use as a novel treatment modality for benign gynecologic conditions such as uterine fibroids.

Recent Findings Computerized searches of Medline and PubMed were conducted using the key words "stereotactic radiosurgery," "CyberKnife®," "uterine fibroids," and "radiation therapy." References from identified sources were manually searched to allow for a thorough review. Data from relevant sources was compiled to create this review article.

Summary Stereotactic techniques have not only significantly reshaped the field of neurosurgery from open to noninvasive treatment, but also has impacted the field of radiation oncology by improving precision and reducing radiation exposure of normal tissues. Stereotactic radiation has proven to be a safe and effective method for the treatment of both benign and malignant conditions. Over the past two decades, new technologies have expanded the application of stereotactic radiosurgery to include spinal, renal, cardiac, lung, liver, prostate, and gynecologic cancers, and very recently even for the treatment of some non-neoplastic conditions such as cardiac arrhythmias. With success in so many disciplines, it is proposed that stereotactic radiosurgery may be a promising tool for the treatment of benign gynecologic conditions. Additional clinical experience is needed to further define the safety and efficacy of this proposed new treatment paradigm.

Keywords Stereotactic radiosurgery · Radiation therapy · CyberKnife® · Uterine fibroids · Leiomyoma

Introduction

The need to improve and deliver the best care with the lowest possible morbidity has repeatedly redefined surgery through the ages. Ultimately, it was Swedish neurosurgeon Lars Leksell that envisioned destroying brain tumors, and even treating non-neoplastic brain disorders, without utilizing any open "conventional" surgery. With the goal of obviating the morbidity of open neurosurgery, Leksell in 1951 conceived of a device that might ablate lesions deep in the brain by using external frame-based image directed targeting and coined the term stereotactic radiosurgery (SRS) to describe the accompanying procedure [1]. By converging numerous beams of high-energy ionizing radiation into an intracranial target, he reasoned it might be possible to destroy a pathologic brain lesion without damaging crucial nearby anatomy [1]. A subsequent major iteration on Leksell's original concept in the 1990s resulted in the first frameless image-guided radiosurgical device, The CyberKnife robotic radiosurgery system (Cyberknife→ Accuray Inc. Sunnyvale, CA, USA developed by John Adler MD). The Cyberknife ushered in a new era of precision image-guided radiation and has enabled the noninvasive treatment or ablation of pathologic lesions anywhere in the human body. This device uses a compact 6 megavolt (MV)

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✉ Camran Nezhat
camran@camrannezhatinstitute.com

1 Center for Special Minimally Invasive and Robotic Surgery, Camran Nezhat Institute, 900 Welch Rd. Suite 403, Palo Alto, CA 94304, USA

2 Stanford University Medical Center, Stanford, CA, USA

3 School of Medicine, University of California, San Francisco, CA, USA

4 Medicines360, San Francisco, CA, USA

5 Harvard Medical School, Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA

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photon linear accelerator to generate high-energy photon beams, which can be directed towards a target using a highly flexible and accurate robot arm. Using image-guidance, the robotic arm can track and target a lesion with sub-millimeter precision, both with and without implanted radio-opaque fiducial markers. With the development of the CyberKnife, it became possible to accurately administer ablative radiation to a specific target while leaving nearby normal tissues largely unaffected. This new generation of precision radiation, variably termed stereotactic radiosurgery (SRS) when performed as a single-dose or stereotactic radiotherapy (SRT), when administered with 1-5 treatments opened new vistas for treating a wide range of human disease. The Cyberknife is now one of the multiple systems that can accurately deliver SRS or SRT [2•].

As the application of SRS and SRT has expanded over the past two decades, the treatment of spinal, renal, cardiac, lung, liver, prostate, and gynecologic cancers has become increasingly more commonplace; recent articles suggest that even cardiac ablation for arrhythmias may soon move from an investigational treatment into everyday clinical practice [3]. With so much success in so many disciplines, it is conceivable that SRS and/or SRT could be a tool for the treatment of benign gynecologic conditions such as uterine fibroids and other benign tumors currently managed by surgery.

Uterine fibroids are the most common benign tumors of the female reproductive system with a cumulative incidence ranging from 70 to 80% of women in the childbearing years [4]. In addition, Baird et al. found the incidence of uterine fibroids increased to more than 80% by age 50 in African-American women, compared to 70% in Caucasian women [4]. Although most uterine fibroids are asymptomatic, 25% of women have symptoms that impact activities of daily living [5•]. The presence of these tumors can lead to abnormal uterine bleeding and subsequent anemia, pelvic pressure/pain, voiding dysfunction, or infertility [3]. The tumors may arise anywhere in the myometrium and thus treatments need to be individualized based on patient symptoms. Moreover, Peddada et al. reported an average growth rate of 9% over 6 months in young women, and as women delay childbearing, the risk of developing uterine fibroids increases [6].

Among the 600,000 hysterectomies performed every year, approximately one-third are performed for uterine fibroids [7]. The estimated annual direct costs (surgery, hospital admissions, outpatient visits, and medications) and indirect costs including obstetric outcomes attributed to uterine fibroids in a 2011 publication was $5.9–34.4 billion [7]. In addition, several operative complications must also be acknowledged. Given that decreasing the number of hysterectomies could potentially reduce both healthcare costs and treatment-related morbidity, it would seem highly desirable to investigate and validate new therapeutic approaches. With this objective in mind, new technological advances, such as SRS or SRT, merit consideration as an alternative treatment for uterine fibroids. Our aim in the current report is to broadly review the safety and efficacy of SRS especially in benign disease and discuss possible applications to gynecology.

For the current study, computerized searches of Medline and PubMed were conducted in November 2018 using the key words "stereotactic radiosurgery," "radiation therapy," "CyberKnife®," and "uterine fibroids." References from identified sources were manually searched and reviewed to allow for a thorough analysis. Data from relevant sources was then manually aggregated to create this review.

Current Management of Uterine Fibroids

Diagnosis and management of uterine fibroids have evolved over time. The standard diagnostic test is transvaginal sonographic imaging. Pelvic MRI with contrast is also employed to delineate the exact location, differentiate a degenerating uterine fibroid from adenomyosis or adnexal mass, and give insight into the possibility of uterine leiomyosarcoma [8].

Symptomatology and fertility preservation dictate the treatment approach. Lack of prospective studies comparing different treatment modalities creates uncertainty and variability in management. The most commonly utilized invasive treatment options are hysterectomy, myomectomy, uterine artery embolization, uterine fibroid radiofrequency ablation, and MRI-guided focused ultrasound surgery (MRgFUS) [9]. Surgery remains the primary method of treatment as newer medical therapies have yet to prove their effectiveness.

Medical management of uterine fibroids includes high-dose progestins, hormonal IUDs, oral contraceptive pills, tranexamic acid, anti-inflammatory drugs, and GnRH analogs [9]. The only medication that has been shown to decrease uterine fibroid volume is the GnRH analog leuprolide [9]. However, its use is limited due to risks of bone loss and other anti-estrogenic side effects. Other medical management options have only been shown to help with temporary relief of symptoms, but none have shown a definitive cure.

For women with symptomatic fibroids who desire fertility, myomectomy is the gold standard treatment approach [9]. Postoperatively, 67% of patients reported a decrease in dysmenorrhea and up to 90% reported a decrease in menstrual bleeding. However, up to 90% of women also developed adhesions following surgery [9]. Small rates of other postoperative complications occurred including fever, anemia, and pain. Moreover, the recurrence rate of uterine fibroids ranges from 5 to 67% with 3–23% of women requiring reoperation [9]. Pregnancy rates after myomectomy range from 33 to 78% [9].

Although another minimally invasive approach that is most suitable for patients who have completed childbearing is uterine-artery embolization (UAE), subsequent pregnancy has been reported in only 33–50% of cases [10]. UAE involves the transfemoral insertion under fluoroscopic guidance of an angiography catheter into the uterine arteries followed by the bilateral injection of non-biodegradable polyvinyl alcohol [10]. This technique relies on the collateral blood flow to the uterus as a means of protecting the blood supply to the uterus itself; uterine fibroids are supplied by end arteries only. The result of this procedure is necrosis of the embolized uterine fibroid. A 77% decrease in pain, 82% decrease in bleeding, and a 33–75% decrease in uterine fibroid size following UAE has been reported [10]. This procedure is also usually associated with a shorter hospital stay when compared to surgical resection. However, common complications include postembolization syndrome, pain, and fever, sometimes requiring hospitalization for management of vaginal expulsion of submucosal uterine fibroids. Long-term complications include 14% risk of adhesion formation and a 10–25% recurrence rate, with 10–32% of patients ultimately requiring a hysterectomy [11].

Another surgical treatment modality that is gaining popularity is uterine fibroid radiofrequency ablation done either laparoscopically or transcervically. This procedure is recommended for premenopausal women who desire to retain their uterus [12]. A recent small (67 patients) meta-analysis recommended that laparoscopic radiofrequency ablation be limited to non-pedunculated uterine fibroids of less than 6 cm [13•]. This study reports a 1.78% complication rate, uterine perforation being the most serious event [13•]. Even though it has shown to be effective in symptom improvement, re-intervention, most commonly hysterectomy, was found to be 4.8% [13]. Another paper on transcervical, intrauterine sonography-guided radiofrequency ablation demonstrated significant median reductions in total (73.3%) and perfused (73.3%) uterine fibroid volume, menstrual bleeding (72.3%), symptom severity (62.5%), and improvements in health-related quality of life (127%) at 12-month post-ablation.

MRgFUS is an evolving technology that uses accurately focused sonication energy to thermally ablate (with temperatures of 60–100 °C) a target region while sparing normal adjacent tissue [14]. In one study, MRgFUS demonstrated a 4–32% decrease in uterine fibroid size; unfortunately, changes in menorrhagia or dysmenorrhea were not measured [14]. Three percent of patients required blood transfusion following the MRgFUS procedure [14]. Meanwhile, recurrence rates are high with 8–48% of patients being retreated [14]. It is reported that live birth rate following MRgFUS was 41%. Pregnancy complications after both UAE and MRgFUS include miscarriage, preterm delivery, need for cesarean section, and placenta previa.

Stereotactic Radiosurgery

SRS or SRT technologies enable the delivery of high doses of radiation with both great spatial accuracy and a steep dose fall-off outside a radiographically defined target. Such ablative treatment is most commonly administered in a single session (SRS) but larger neoplasms or those near the radiation sensitive anatomy can be treated in up to 5 fractions (SRT). Compared to conventional radiation, SRS enables much higher radiation doses to be delivered, with improved conformality of the dose and sparing of surrounding non-target "normal" tissues. The exquisite precision of SRS even allows safe delivery of repeated courses of radiation to anatomic sites in close proximity to previously irradiated sites, a feat historically less feasible with conventional radiation techniques [15]. There is an inverse correlation between tumor size and favorable treatment outcome with SRS/SRT of pelvic gynecologic tumors [16, 17]. One study of recurrent pelvic gynecologic tumors treated with SRT achieved exceptional local control, low instances of toxicity, and overall survival after 2 years of 89% in tumors under 30 cm^3 compared to only 12% 2-year survival in large tumors over 30 cm^3 [16]. Thus, SRS/SRT for pelvic tumors is ideally suited for smaller tumors. Notably, the toxicity profile of SRS or SRT compared to conventional radiotherapy is usually mild and self-limited. In the pelvic and abdominal area, reported grade 1–2 toxicities include fatigue, diarrhea, dysuria, nausea, and sexual side effects, with few grade 3 or higher adverse events [16].

Numerous publications have shown that SRS or SRT can safely and efficaciously treat both benign and malignant lesions such as brain tumors, melanoma metastases, trigeminal neuralgia, arteriovenous malformations, renal artery hypertension, back pain, cardiac arrhythmias, and lung, kidney, liver, prostate, and gynecologic cancers [4, 5•, 7, 19]. Because ionizing radiation has its greatest cytotoxic effects on rapidly dividing tissues like cancer, SRS and SRT is most commonly used to treat malignancies. Nevertheless, there is a wealth of literature that describes the ablative use of radiotherapy, including SRS and SRT, to effectively ablate slow-growing malignancies as well as benign lesions, and even in some cases, normal tissue [18].

Stereotactic Radiosurgery Application for Benign Lesions

Radiation therapy has been used with varying success for several benign processes, including paraganglioma, arteriovenous malformation, trigeminal neuralgia, heterotopic ossification, gynecomastia, keloid, cardiac arrhythmias, and benign brain tumors such as vestibular schwannomas and meningiomas. While external beam radiation therapy using simple beam arrangements that expose normal tissues to therapeutic doses has been historically used, more conformal radiation techniques such as intensity-modulated radiotherapy (IMRT) or image guided radiotherapy (IGRT) have been employed to reduce normal tissue exposures. Stereotactic radiosurgery/radiotherapy (SRS/SRT) have emerged as the most conformal radiation techniques used for brain lesions and other localized lesions in the body without the toxicity of whole organ exposure.

For example, with a greater than 20-year track record, Cleveland Clinic has shown SRS to be a safe and effective tool for managing benign highly vascular neuroendocrine tumors.

When compared to open surgical resection, SRS has less morbidity, particularly regarding reducing cranial nerve dysfunction. The authors concluded in their report that SRS should be considered a first-line option for vascular glomus jugulare tumors (paraganglioma) in patients [19].

Researchers at New York University have proposed that SRS should be deemed the primary standard of care for most patients with benign brain tumors such as vestibular schwannomas and meningiomas. Indeed, long-term control rates exceeding 90%, better cranial nerve function, generally no hospital stay, and shorter disability time have all been reported with SRS, while simultaneously costing less than surgical resection [20]. Meanwhile, University of Pittsburgh analyzed 972 patients with 1045 benign meningiomas in a cohort that included 70% women, 49% with a history of prior resection, and 5% having a history of prior conventional radiotherapy. At 10-year follow-up, grade 1 meningiomas were controlled in 91% of the patients and primary tumors in 95% [20]. SRS has also been used in the treatment of pituitary adenoma. In 512 patients with pituitary adenoma, a recent multicenter trial reported a 93% success rate [1].

Seeking to ablate essentially normal tissue, SRS has been utilized to treat both cardiac arrhythmias and temporal lobe epilepsy [3, 21]. To date, there are twenty-seven patients who were successfully treated for ventricular tachycardia and two patients who were treated for atrial fibrillation. Active trials are still underway [3, 22]. Barbaro et al. reported treating 31 patients with SRS while 27 patients underwent anterior temporal lobectomy for patients with temporal lobe epilepsy [21]. They concluded that both approaches were effective, and 52% of patients were seizure free with the non-invasive SRS approach [21].

Even with SRS or SRT, there may be adverse events related to treatment.

Radiation-induced tumors can be a concern; although given the small focused areas being treated with radiation when using SRS or SRT, this risk is thought to be less than when using conventional external beam radiation therapy. In the series of meningioma patients described above, there were no cases of radiation-induced tumors. However, there are a handful of other reported cases, including an SRS-associated glioblastoma and the delayed malignant transformation of a chondrosarcoma post SRS [20]. Other side effects depend on the site being treated. For example, for pituitary adenomas treated with SRS, new-onset hypopituitarism was observed in 0–40% of patients, with a mean of 8.8% [1]. Some have suggested decreasing the radiation dose to the immediately adjacent pituitary stalk to offset this risk.

Radiation Experience in Benign Gynecology

X-rays were discovered in 1895. Shortly thereafter Morton and Pfahler tested the effect of radiation on uterine fibroids. Since that time, multiple historical studies have described the efficacy of radiation treatment for benign gynecologic conditions. Radiation has the effect of eliminating bleeding and causing involution of uterine fibroids. While the mechanism of effectiveness of radiation is unclear, it is felt that radiation most likely works to obliterate blood vessels. However, the hormonal effect of the radiation resulting in ovarian castration is equally plausible. Hunter et al. treated reproductive-aged women in the 1920s with menorrhagia using radium or external radiation, which successfully decreased menorrhagia in over 95% of these patients [23]. Ryberg et al. published the largest study of 933 women treated with radium between 1912 and 1977 for menorrhagia with intracavitary brachytherapy, external radiotherapy, or a combination of both [24]. They reported a cure rate for menorrhagia of 48%. However, menopausal symptoms developed in 23% of patients and calculated a relative risk of 1.19 for the development of secondary malignancy [25]. Due to the high risk of ovarian failure, women less than 50 years of age could experience a greater risk of cardiovascular death and accelerated osteoporosis [25]. Additionally, a number of these patients may have had undiagnosed malignancies as a cause of their menorrhagia. Heyerdahl et al. treated thirty uterine fibroid patients with either roentgen rays ($n = 25$) or roentgen plus radium ($n = 5$) [26]. Seventeen patients were followed for 9years and 7 patients for 5 years after receiving the treatment. Of these patients, 0.2% required surgery and 83.3% had cessation of menses with almost complete resolution of uterine fibroids [26].

There are also several other smaller series and case reports published describing the use of radiation treatment for benign gynecologic conditions. In 2016, Zhang et al. described a case report of an intravenous fibroid that had recurred after successful en bloc resection [27]. At the time of recurrence, this patient was not a surgical candidate due to prior history of deep vein thrombosis and postoperative deconditioning. External radiation therapy using 15-MV X-ray radiation (Varian 21EX Palo Alto, CA) was used at a dose of 2.0 Gy per fraction, 4 fractions per week, with a total dose of radiation of 45 Gy [27]. Although the total response of the intravenous fibroid was slow due to the slow growth of the tumor, over a 6-month period the patient achieved a total response. Zang et al. stated that because benign tumors grow slower than malignant tumors, lower radiation doses could be used with fewer side effects. They concluded the use of radiation therapy was a feasible and effective alternative for inoperable intravenous fibroids [27].

However, radiotherapy in the pelvic and abdominal region can cause a variety of acute side effects including diarrhea, bladder irritation, cytopenias, skin irritation and hair loss, vaginal irritation, nausea, and fatigue, most of which are self-limited [28]. Late side effects can include permanent hair loss or skin changes, ovarian failure, vaginal stenosis, proctitis (e.g., rectal bleeding, diarrhea, bowel frequency), cystitis (e.g., urinary frequency/urgency, hematuria), and rarely, bowel/bladder obstruction, perforation or fistula formation, pelvic or spinal insufficiency fractures, or secondary malignancies [28]. One of the most concerning late side effects is the possibility of a radiation-induced second malignancy. Although the overall risk is low, the delayed latency of radiation-induced malignancies extending beyond 2–3 decades has especially detrimental implications for young women. Indeed, it was the concern for radiation-related carcinogenicity that increasingly stigmatized and decreased the use of radium and ionizing radiation for benign gynecologic conditions in favor of surgery and other ablative techniques [23].

Who Might Be a Candidate for Gynecological Treatment Via Radiosurgery and How Would This Be Carried Out?

Potential candidates for SRS or SRT may include patients with symptomatic benign uterine fibroids who are poor surgical candidates, or who refuse current interventions. Optimally, patients would be enrolled in a prospective trial and/or registry to assess the safety and efficacy.

It is well-established that total body radiation induces ovarian failure in almost 90% of women treated with doses as low as 3.6 to 7.2 Gy [17]. Given the precision of SRS/SRT compared to historical radiation techniques for uterine fibroids, the dose to the ovaries could be substantially reduced with likely preservation of ovarian function. However, for caution, the initial patients for uterine fibroid SRS should be post childbearing or should undergo oocyte or embryo cryopreservation prior to any radiation treatment. While full pelvic irradiation is associated with smaller uterine volume and increased risk of miscarriage, preterm labor, and low-birth weight fetuses, it is unclear whether SRS/SRT would show similar results [29]. In the abundance of caution, patients considered for this technique should be counseled about these risks.

Were radiosurgery to be performed for uterine fibroids, a necessary first step would involve the placement of transvaginally or transcervically placed fiducials, near the target uterine area of interest under image guidance using any combination of pelvic MRI, CT scan, or sonography. These initial imaging studies would be used to assess the impact uterine, bowel and other pelvic organ motion, in addition to mapping the planning target volumes and defining the adjacent organs at risk for the radiation treatment plan. Once a radiation treatment plan is approved by the treating physician, the ablative procedure could be performed using the Cyberknife robotic system or another SRS/SRT delivery system with image guidance starting at doses of 15–30 Gy in 1–5 fractions. Real-time image guidance would be used, either using fiducials for localization, or soft tissue structures in the pelvis, to ensure accurate patient and target positioning prior to and during treatment. Treatment times may vary from 20 to 90 min based on the treatment delivery system, the treatment plan, the lesion target size, and the location. The non-invasive treatment procedure would require no sedation. Once completed, the patient is typically able to immediately ambulate. If there is a temporary fiducial marker in situ, it could be immediately removed afterwards. Patients can then usually return home after brief observation.

Conclusion

SRS and SRT is a well-established technology and therapy that continues to evolve and develop and can be used to safely and effectively treat a broad array of benign and malignant conditions. With the success of SRS/SRT in many other benign conditions and historically proven efficacy of radiation for uterine fibroids, it is conceivable that SRS or SRT could be successfully deployed in the contemporary treatment of benign gynecologic conditions. Further studies are necessary to define safety and efficacy in larger populations of patients and to better understand whether this approach can mitigate the risk of ovarian failure and secondary tumors compared to historical radiation series.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclosure Dr. Gibb's have received honoraria for lectures in the past 12 months from Accuray, Inc., the manufacturer of the Cyberknife.

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