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AUTHOR(S)

Timothy Murray, Frank Doyle, Michael J. Lee

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TITLE: Transarterial Embolization of Angiomyolipoma - A Systematic Review

AUTHORS AND AFFILIATIONS:

Dr Timothy Murray, (Corresponding Author)

Department of Radiology,

Beaumont Hospital,

Dublin 9,

Ireland.

Ph: +353 1 809 3000

Email: timothymurray@rcsi.ie

Dr Frank Doyle,

Division of Population and Health Sciences,

Royal College of Surgeons in Ireland,

St Stephens Green,

Dublin 2,

Ireland.

Ph: +353 1 402 2718

Email: fdoyle4@rcsi.ie

Prof Michael Lee,

Department of Radiology,

Beaumont Hospital,

Dublin 9,

Ireland.

Ph: +353 1 809 3000

Email: mlee@rcsi.ie

RUNNING-HEAD: Transarterial Embolization of Angiomyolipoma

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ABSTRACT:

Introduction: Transarterial embolization (TAE) is increasingly used in the management of renal angiomyolipoma (AML). The level of evidence establishing the safety and efficacy of TAE has not increased in parallel.

Materials and Methods: Using the MOOSE criteria, a systematic review of transarterial embolization of angiomyolipoma was performed to establish procedural safety and efficacy. MEDLINE PubMed search revealed 1739 publications, of which 31 studies met eligibility criteria.

Results: 524 cases of TAE of AML were included. Self-limiting post-embolization syndrome occurred following 35.9%. Further morbidity occurred in 6.9%. No procedural mortality was reported. At a mean follow-up period of 39 months, mean size reduction was 3.4 cm (-38.3% of AML diameter). Unplanned repeat embolization or surgery was required in 20.9% during this period. The most frequent indications for repeat procedures include angiomyolipoma revascularization (30.0%), unchanged or increasing size (22.6%), refractory or recurring symptoms (16.7%), and representation with acute retroperitoneal hemorrhage (14.3%). A combination of two or more embolic agents was used in 46.8%, ethanol monotherapy in 41.7%, coil monotherapy in 6.2%, and foam or microparticle monotherapy in 5.2%.

Conclusions: Transarterial embolization of angiomyolipoma demonstrates low rates of mortality and serious complications. Retreatment rates and size reduction at a mean follow-up duration of 39 months are presented. Longitudinal data assessing long-term size reduction and retreatment rates are lacking, recommendations guiding the indications for transarterial embolization and clear follow-up require further longitudinal data.

Introduction

Background

Angiomyolipoma is a benign renal tumour, accounting for 0.3-3% of all renal masses.^{1, 2} These tumours are composed of blood vessels, fat and smooth muscle in varying quantities.³ Angiomyolipomata are benign, however size increase of 0.088-0.427 cm/year is reported, and can result in mass effect.^{4, 5} Distorted vascular architecture can additionally predispose angiomyolipoma to active retroperitoneal hemorrhage.⁶ Angiomyolipoma has a prevalence of 0.02-0.1% in males, and 0.22-0.29% in females.^{7, 8} 20% of patients with angiomyolipoma have TSC, an autosomal-dominant multi-organ disorder predisposing to benign tumour formation. Amongst all patients with TSC, 50% develop angiomyolipoma in their lifetime.⁹ The remaining 80% of cases of angiomyolipoma are sporadic.^{6, 8}

Current Management Strategies of Angiomyolipoma

Prior to 1976, 93% of sporadic angiomyolipoma were treated with open total nephrectomy.⁶ Angiomyolipomata were commonly excised as a malignant renal lesion could not be excluded. Angiomyolipoma can now be confidently diagnosed at imaging.¹⁰ Even in cases of small or fat-poor angiomyolipomata, magnetic resonance imaging demonstrates a specificity of 99%.¹¹ Many centers now favor transarterial embolization of angiomyolipoma, and reserve surgery for patients with refractory symptoms, complex renal artery anatomy, failure of embolization, and rare cases of diagnostic uncertainty.¹² The adoption of embolization as the treatment of choice has not been paralleled by a strengthening of the evidence supporting its use. Small studies, primarily case series report embolization as the sole form of therapy has a reported success of 86-90%, with a morbidity of 10-17%.^{1, 9} It permits preservation of uninvolved renal parenchyma. This is significant in patients

with tuberous sclerosis, who often have bilateral or multiple renal angiomyolipomata, requiring a conservative approach to any renal intervention.

There is a paucity of literature comparing nephrectomy and nephron-sparing surgery with transarterial embolization in the management of angiomyolipoma.^{2, 9} In the last decade, successive studies have established the role of chemotherapy, based on mTOR inhibitors such as sirolimus, in the management of patients with TSC-associated angiomyolipoma. The tumour biology in these patients demonstrate over-activation mTOR complex 1 (mTORC1), and mTor inhibitors have demonstrated size-reduction in TSC-associated angiomyolipomata.^{13, 14} The use of chemotherapy, however, is not widely employed in the more common, sporadic form of AML. Future advances may exploit the recently proven over-expression of selective hormonal receptors through hormonal regulation.¹⁵ More recently, several small case series have investigated the role of radiofrequency ablation (RFA), however little long term follow-up is available.^{16, 17}

Current treatment strategies are twofold. In patients with active retroperitoneal hemorrhage, or with a symptomatic angiomyolipoma, intervention is widely advocated.¹⁸ In 1986, Oesterling et al. reported AML over 4 cm were more likely to present with active retroperitoneal hemorrhage. This size-threshold for treatment has been widely adopted, however, it does not account for factors which are now known to be linked with active retroperitoneal hemorrhage. To the authors' knowledge, no randomized controlled trials exists comparing embolization with placebo or with interventional or surgical management. Additionally, few studies employed controls or present long-term post-procedural follow-up data. We aimed to review the literature with the primary aim of establishing the morbidity and mortality of transarterial embolization, whilst assessing size-reduction and the need for repeat procedures, to establish the safety and success of this treatment.

Materials and Methods

A MEDLINE® search was performed to assess articles relating to renal angiomyolipoma. The primary endpoints were the morbidity and mortality of angiomyolipoma embolization, technical success of embolization, the need for repeat procedures and size reduction. All published full-text English language publications were included. Exclusion criteria included single patient case-reports, studies assessing surgery only, and studies without electronic editions. Several studies combined contemporary case series from their institution with historical case series from the literature for analysis. In such publications, where data from individual studies could not be extracted, or was insufficiently presented to permit analysis, these publications were not included.¹¹²¹⁹

The current literature is overwhelmingly represented by retrospective single center reviews, with several prospective reviews and multi-center retrospective reviews. Only one study was identified employing case controls, thus prohibiting quantitative synthesis and meta-analysis. Qualitative review was employed using the MOOSE criteria; a reporting guideline tool designed for analysis of observational studies in epidemiology.²⁰ As a result of the heterogeneity of patients, outcomes and data collection methods, interpretation was confined to pooled descriptive analysis.

Results

Review of the Literature

A MEDLINE search using the term renal angiomyolipoma was performed on 13th May 2013, returning 1739 articles. 31 studies matched eligibility criteria, including 802 patients, of which 524 (65.3%) underwent embolization. Many of these studies additionally reported patients with

angiomyolipoma who underwent alternate or conservative management and were presented in the same series, and these 278 non-embolization patients were therefore excluded from primary endpoint analysis. All included studies represented Level IV evidence. The 31 included studies were published from 1986 to 2013, however 27 of these studies were published after the year 2000, accounting for 93.1% of patients. The eleven largest series included were all published since 2006.

Procedural Morbidity and Mortality

Mean post-embolization follow-up period was 39 months. There were no intra-procedural mortalities or fatal complications. In 23 studies (n=304 patients) post-procedural morbidity was described. Post-embolization syndrome, a self-limiting constellation of symptoms including fever, nausea, vomiting and pain within the first 72 hours, occurred following 35.9% of procedures (n=109). Further post-procedural morbidity occurred in 6.9% of patients (n=21). This included non-target embolization (2.3%), respiratory complications (2.0%), abscess formation (1.6%), active retroperitoneal hemorrhage (1.0%), allergic reactions (0.6%), urinary retention (0.6%), urinary tract infections (0.3%), femoral artery damage requiring repair (0.3%) and renal artery spasm (0.3%).

Treatment Success and Need for Repeat Procedures

Mean technical success (complete intra-procedural occlusion of arterial inflow) was obtained in 93.3% of embolizations. In 263 cases providing both follow-up duration and size, angiomyolipoma reduced by a mean 3.4 cm (-38.3%) at final follow-up averaging 39 months. Several studies reported individual cases where selective embolization was planned in two stages to maximize renal preservation where renal function was impaired, typically in the context of multiple TSC-associated angiomyolipoma.^{21, 22} All remaining procedures, however, were performed view to complete embolization at the first attempt. Unplanned repeat procedures were performed in 20.9% of patients

(n=103 of 494 cases). The indication for repeat procedure was specified in 84/103 patients, causes include angiomyolipoma revascularization on follow-up imaging (30.0%, n=25), unchanged or increasing size (22.6%, n=19), refractory or recurring symptoms (16.7%, n=14), representation with acute retroperitoneal hemorrhage (14.3% n=12), failure to devascularize lesion (4.8%, n=4), failure to control active retroperitoneal hemorrhage (4.8%, n=4), failure to identify or cannulate hemorrhagic vessel (4.8%, n=4), concern over malignancy (2.4%, n=2), and contrast-sensitization requiring postponement following corticosteroid cover (1.2%, n=1).

Embolization Agent

In 367 patients, the method of embolization was provided. A combination of two or more embolic agents was used in 172 patients (46.8%). Ethanol monotherapy was used in 153 patients (41.7%). Coil monotherapy was used in 23 patients (6.2%). Foam or microparticle monotherapy was used in 19 patients (5.2%). These studies typically did not provide individualized data on specific embolization agents. Many studies also used of different agents within the same case-series, further limiting assessment of the efficacy of individual agents. Studies using exclusively ethanol monotherapy (7/31 studies) had a mean technical success of 95.5% (range 83.3%-100%), retreatment rate of 14.7%, morbidity of 44.9% and a mean size reduction of 2.3 cm. Studies using exclusively two or more agents per embolization (6/31 studies) had a mean technical success of 95.0% (range 89%-100%), retreatment rate of 24.3%, morbidity of 26.4% and mean size reduction of 4.6 cm.

Discussion

Transarterial Embolization as a Treatment Modality

The implications of this study of transarterial embolization of angiomyolipoma are a high technical success (93.3%), a low retreatment rate (20.9%), and a mean size reduction of 3.4 cm. These results are based on mean follow-up period of 39 months, and long-term data evaluating retreatment rate and sustained size-reduction are lacking. Selected small studies with longer follow-up have demonstrated increasing retreatment rates with longer follow-up. This may indicate retreatment rate increases over time.²³

Low procedural mortality (0%) compares with a 0.9% thirty-day mortality associated with nephrectomy.²⁴ Embolization is associated with high rates of adverse affects (42.8%), however the majority are self-limiting post-embolization syndromes (35.9% of all embolizations). Routine post-embolization syndrome prophylaxis, including antipyretics, antiemetics and analgesia may have a role in peri-procedural management. Several individual studies have reported lower rates of post-embolization syndrome with super-selective embolization.^{23, 25} Further morbidity was uncommon, occurring in only 6.9% of all embolizations. This compares with 12% morbidity associated with partial nephrectomy for angiomyolipoma, which are typically more serious.^{12, 26}

Techniques for embolization include selective and super-selective techniques, embolizing from varying points within the renal arterial tree. Furthermore, there exists a variety of embolization techniques, including ethanol, coils, foam and microparticles, which can be employed alone or in combination. Several studies have compared varying size of embolic agents. It has been suggested that combination therapy may be most effective in reducing retroperitoneal hemorrhage, with microparticle embolization of the distal vascular bed to prevent retrograde filling, and coil occlusion of arterial inflow in an effort to both occlude perfusion and reduce arterial inflow

pressures.²⁷ The small number of cases in studied case series, and presence of multiple confounding factors between studies, does not permit strong recommendations in favor of any one embolization agent at this time.

Study Limitations and Bias

With the exception of a single study, no case-controls were identified to assess for confounding. This is a fundamental weakness of case-series. Several studies completed stratified analysis, which can identify confounding or effect modification, however this was not performed in the majority of studies. An unknown source of bias was the analysis of published series reporting intervention. While there are papers predating intervention, there was no large, contemporary control group with which to compare results from patients undergoing intervention. Comparison with historical control groups is possible, however given advances in all aspects of patient care, this is of questionable applicability. Several studies evaluated procedural complications according to the Society of Interventional Radiology (SIR) Classification System for Complications by Outcome. Many studies, however, did not use such measures, and reported complications in an arbitrary or case-by-case descriptive manner, exposing to detection bias. Due to a lack of individualized patient data, assessment and comparison of treatment agents is limited. Indeed, even within specific treatment agents, it has previously been demonstrated that even factors such as particle size of specific embolic material may affect outcomes.³⁰ Attrition bias was possible as many retrospective case-series reported the duration of follow-up, but did not specify if the end of follow-up was planned, or if patients were lost to follow up. The risk in individual studies varies however in the majority the risk of attrition bias was unclear. The short mean follow-up time is significant limitation when studying a slow-growing process such as angiomyolipoma. Retreatment rates at a mean of 39 months likely underestimate the lifetime retreatment rates, and further longitudinal data are required to predict the long-term retreatment rate of embolization.

Selecting Patients Who May Benefit from Treatment

The presence of symptoms, and a size exceeding 4 cm, are widely cited justifications for intervention.¹⁸ Current practice is based on a seminal paper from Oesterling et al, and is largely unchanged since 1986. In lesions less than 4 cm, only 23% of patients develop symptoms and 13% of cases present with active retroperitoneal hemorrhage. In lesions greater than 4 cm, this increases to 82% of patients presenting with symptoms, and 51% of patients presenting with active retroperitoneal hemorrhage.⁶ Our understanding of the disease biology, and the management of angiomyolipoma, has since changed significantly since this time, however. The use of a treatment size threshold of 4 cm has been examined recently by both Mourikis et al. and Dickinson et al, who have proposed the use of 8 cm as a size-threshold.^{18, 28}

As imaging has progressed, tumor vascularity can now be assessed, and aid in treatment decision-making. Yamakado et al reported a significant positive association between aneurysm formation and active retroperitoneal hemorrhage.²⁹ There may be a role for angiography, either conventional renal angiography or renal CTA, in informing treatment decisions, particularly in smaller, asymptomatic angiomyolipoma where surveillance may be considered.

Treatment selection and timing in patients with TSC is complicated by the frequency of bilateral renal involvement, neurological or multi-system comorbidities, and the potential for atypical acute presentations. The sequela of urgent nephrectomy in a patient with multiple bilateral tumours can be profound, as poor or absent renal reserve may precipitate long-term renal replacement therapy. Pharmacological inhibition of tumor growth in these patients using mTor inhibitors may offer a systemic treatment for these multifocal lesions, with transarterial embolization employed for large angiomyolipomata, active retroperitoneal hemorrhage or symptomatic lesions. Nelson et al note the

rarity of acute retroperitoneal hemorrhage of angiomyolipoma in pregnancy, and suggest a conservative approach may be warranted during pregnancy. Where pregnancy is planned, prophylactic embolization may be warranted only in larger tumors.⁹

Role for surveillance and post-procedural follow-up

There is little consensus on the need, duration and modality of follow-up. In light of a retreatment rate of 20.9% at a mean follow-up period of 39 months, post-procedural follow-up over this period may be of value. The need for longer term follow-up is not clear. Clinical follow-up permits assessment of symptomatology, hematuria and systemic symptoms, whilst radiological follow-up allows assessment of size, vascularity and the presence of aneurysms. Ultrasound, CTA and conventional angiography have all been employed. Angiographic techniques permit the simultaneous assessment of both size and aneurysm formation. Ultrasound is non-invasive and requires no ionizing radiation or iodinated contrast, which may be of relevance in cases of renal impairment, as is often seen in TSC. Ultrasound has limited sensitivity of dedicated angiographic studies in the detection of aneurysm formation, however. A combination of radiological modalities and periodic clinical follow-up may be optimal following embolization.

Conclusion

TAE is associated with low procedural mortality (0%). Post-embolization syndrome is common (35.9%), and routine prophylaxis may be appropriate. Other forms of morbidity occur in 6.9%. Repeat embolization or surgery was required in 20.9% of cases. Mean follow-up duration remains short (39 months), and long-term follow-up data are required.

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AML = Angiomyolipoma

TAE = Transarterial Embolization

TSC = Tuberous Sclerosis Complex

CTA = Computed Tomography (CT) Angiography