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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Elective Regional Therapy Treatment for Hepatic Adenoma

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ABSTRACT

Background. Locoregional therapy treatments for hepatic adenoma (HA) are typically limited to selective hepatic arterial embolization (HAE) to control acute hemorrhage. This systematic review sought to report the utilization of HAE and ablation for non-emergent treatment of HA.

Methods. A PubMed query identified studies reporting ablation or embolization for HA patients. Abstracts were screened to exclude studies with only patients managed for acute hemorrhage. Outcomes of interest included rate of success, complications, and repeat procedures.

Results. Of 209 initial search results, 33 full-text publications were reviewed, and 10 were selected after applying the exclusion criteria. All were published from 2005 to 2016. A total of 105 patients were included, of which 66 patients with 138 adenomas underwent elective locoregional therapy treatment. The mean size of treated adenomas was 2.9 (range 0.8–8.3) cm. HAE was utilized in 25 patients with 58 adenomas, whereas 35 patients with 68 adenomas underwent radiofrequency ablation. Six patients with 12 adenomas received microwave ablation. Most patients were female (89/105), and adenomas were associated with oral contraceptive use or hormonal therapies in 49 of 105 patients. Success was reported in 115 of 138 first-time procedures, and repeat procedures were needed after 18 of 138. Mean follow-up time was 36.4 months, with two complications.

Conclusions. Reports of elective locoregional therapy for the treatment of HA are limited to case reports and small institutional series. In the select patients treated, outcomes are acceptable, with low rates of repeat procedures or complications. This systematic review warrants further discussion and broader consideration for the treatment of HA.

Hepatic adenomas (HA) are a rare and benign disease that primarily affect a young and otherwise healthy patient population, but the risk of hemorrhage and malignant transformation makes identification and treatment crucial. Surgical resection is typically reserved for tumors greater than 5 cm, unless other risk factors of glycogen storage disease, such as male gender and steroid use, are present.[1] Management is typically selected based on the tumor size and anatomic location. For many patients, surgical resection remains the standard intervention for HA because of the potential risk for hemorrhage and/or malignancy, but orthotopic liver transplantation also may be considered for adenomatosis.[2] Smaller HA with a low risk of hemorrhage may simply undergo observation.[3] Patient demographics may influence the course of management, and the treatment modalities available for HA continue to evolve.

The concept of locoregional treatments for liver tumors has evolved significantly over the past 30 years. Ablation and embolization have been widely accepted for the management of hepatocellular carcinoma and other hepatic malignancies, and these techniques are now being recognized for treatment of hepatic adenoma. Selective hepatic arterial embolization (HAE) techniques often are considered palliative in oncologic patients but bland particle embolization may serve a more primary role in HA management. Given the high mortality rate for emergency resection in the setting of HA rupture, arterial embolization has been well-described for the treatment of acute tumoral hemorrhage.[4] Some limited series have reported elective embolization of HA as a bridge to resection, sometimes

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leading to the avoidance of surgery. The success of radiofrequency ablation (RFA) for hepatic malignancy has led to its possible use for HA, and some have proposed selective ablation as an alternative to surgical resection.

Although reports are limited, elective embolization has been described as a useful tool in reducing the size and hemorrhagic potential of large HA before surgery.[5,6] Studies reporting ablation as an alternative to surgery often support its use for tumors less than 5 cm or as an intraoperative complement to lobectomy in patients with adenomatosis.[7–9] Ablation also may be an option for patients pursuing pregnancy or those especially concerned about aesthetics or the invasiveness of resection.[10,11] This systematic review sought to report the utilization and outcomes following nonemergent treatment of HA by locoregional therapy techniques, including HAE, RFA, and microwave ablation (MWA).

METHODS

Study Selection

Studies were selected according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[12] PubMed was searched for studies published in English up to October 2017. The search query utilized ("Appendix 1") was designed to capture all reports of embolization or ablation techniques used for the management of hepatic lesions. The PRISMA diagram details the selection process for the included studies (Fig. 1). All studies mentioning the use of ablation or embolization for the treatment of hepatic adenoma specifically were considered for inclusion. To ensure commonality of locoregional therapy techniques, studies published before 2002 were excluded. Studies were excluded if all patients were treated for emergent hemorrhage only.

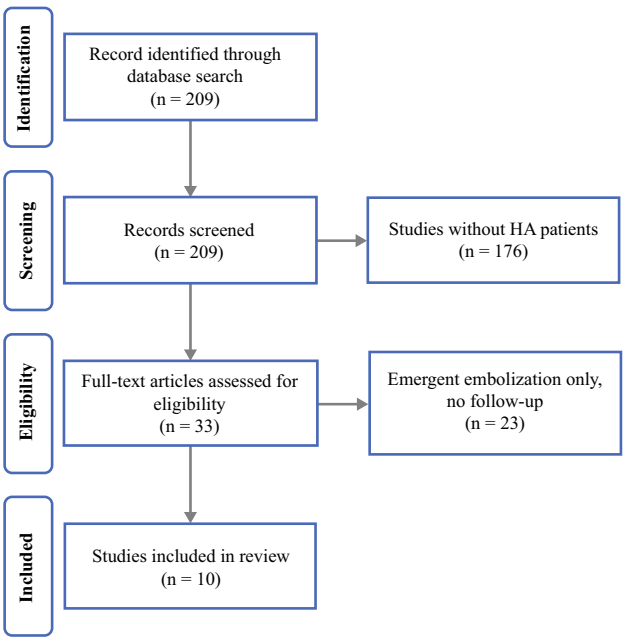

FIG. 1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart for the current review

Data Collection and Analysis

For each study included in the review, the following baseline data were extracted: patient age, gender, suspected etiology of HA diagnosis, number of tumors, size of tumor, and treatment received (RFA, MWA, or HAE). Outcomes data included: incidence of complication, type of complication, success rate, follow-up time, incidence of repeat procedure.

Baseline data and outcomes are displayed as originally presented in the source article. Summative results are tabulated as numerators and denominators or mean and median values. Due to significant heterogeneity between studies, no meta-analysis was performed.

RESULTS

Screening and review of abstracts and full texts was completed according to the PRISMA guidelines, as outlined in Fig. 1. Abstracts from the 209 original search results were screened, and 33 full-text articles were reviewed in detail for inclusion. Based on the exclusion criteria detailed above, ten studies were included for quantitative review.[5,8,11,13–19]. All of the studies were published between 2005 and 2016. Table 1 shows the study characteristics and outcomes for the included articles.

A total of 105 patients with 218 HA lesions were included in the review. Of them, 66 patients with a total of 138 HA lesions were treated electively by locoregional therapy techniques (RFA, MWA, or HAE). RFA was utilized for 68 of 138 lesions (49%), HAE was chosen for 58/138 (42%), and MWA was used for 12/138 (9%). The mean patient age was 35.4 years, and 85% of all patients were female. The suspected etiology of disease for 49 of 105 patients (47%) was oral contraceptive pills (OCP) or hormone supplementation. Idiopathic or unknown origin was attributed to 52 of 105 (50%) patients, and the remainder were explained by Turner Syndrome, glycogen storage disease, or hemosiderosis. The mean tumor size treated by RFA was 2.8 cm, whereas the mean was 2.7 cm for MWA and 3.1 cm for HAE. The mean follow-up time after treatment for all patients was 36.4 months. Of the 53 patients for whom complication rates were reported, 2 suffered complications following RFA. One developed

TABLE 1 Baseline data and reported outcomes for the studies included in the current review

Authors	Year	No. of patients	No. of HA	Treatment type	Mean age (year)	Gender	Etiology	Mean tumor size (cm)	Mean follow-up (mo)	Complications	Success rate	Repeat procedures
Atwell et al.	2005	3	3	3 RFA	37	3/3 female	3/3 OCPs	2.3	10.3	0/3	3/3	0/3
Fujita et al.	2006	3	24	15 resected 7 RFA	28	3/3 female	2/3 OCPs 1/3 Turners	2.6	19.3	0/3	6/7	1/7
Rocourt et al.	2006	1	1	1 RFA	13	0/1 female	1/1 Idiopathic	3.5	24	0/1	1/1	0/1
Erdogan et al.	2007	2	2	2 HAE	43.5	2/2 female	2/2 OCPs	5.2	4.5	0/2	2/2	0/2
Rhim et al.	2008	10	12	12 RFA	39.2	5/10 female	10/10 Idiopathic	2.3	17.5	0/10	12/12	0/12
Kobayashi et al.	2009	2	2	2 HAE	31	1/2 female	1/2 GSD, 1/2 hemosiderosis	5.2	18	0/2	2/2	0/2
Deodhar et al.	2011	8	17	17 HAE	39	7/8 female	5/8 hormones	3.6	24	0/8	17/17	1/17
van Vledder et al.	2011	18	45	45 RFA	29.5	18/18 female	17/18 OCPs	3.0	14.5	2/18	26/45	12/45
Karkar et al.	2013	52	100	37 HAE	39	45/52 female	19/52 hormones	2.6	56.4	N/A	34/37	3/37
Smolock et al.	2016	6	12	12 MWA	39.6	5/6 female	4/6 idiopathic, 1/6 OCPs, 1/6 GSD	2.7	18	0/6	12/12	1/12
		Total: 105 RT: 66	218	RFA: 68 HAE: 58 MWA: 12 = 138	RFA: 32.3 HAE: 38.7 MWA: 39.6 All: 35.4	89/105 female (85%)	49/105 (47%) OCP/hormonal 52/105 (50%) idiopathic 4/105 (3%) = Turners, GSD, hemosiderosis	RFA: 2.8 HAE: 3.1 MWA: 2.7 All: 2.9	RFA: 15.7 HAE: 49.5 MWA: 18 All: 36.4	2/53 (4%)	115/138 (83%)	RFA: 13/68 = 19.1% HAE: 4/58 = 6.9% MWA: 1/12 = 8.3% All: 18/138 = 13.0%

HA hepatic adenoma, *RFA* radiofrequency ablation, *HAE* hepatic artery embolization, *MWA* microwave ablation, *OCPs* oral contraceptive pills

cerebral ischemia due to severe intraoperative bleeding during concomitant lobectomy, and the other formed a hepatic abscess following percutaneous ethanol injection. Neither complication was directly attributed to RFA. First-time individual success rate for all adenomas treated was 115 of 138 (83%), determined radiologically by complete elimination or decreased size of the tumor. Repeat procedures were performed following 18 of 138 treatments (13%). RFA was repeated in 13 of 68 treatments (19%), HAE was repeated in 4 of 58 (7%), and MWA was repeated in 1 of 12 (8%).

DISCUSSION

Classical Treatment

Following a radiographic diagnosis of hepatic adenoma, options for management have historically been either observation or hepatic resection. Most propose that gender and tumor size should guide resection.[3] Men have a 6–10x higher malignancy rate than women, and tumors > 5 cm are at greater risk of undergoing transformation.[20] Orthotopic liver transplantation also may be considered for adenomatosis with suspicion of malignant transformation.[2] If imaging reveals a small (< 5 cm) HA, surveillance may be an acceptable course of management coupled with elimination of predisposing risk factors, such as oral contraceptive pills.

Regional Therapies for Hemorrhage

The majority of literature reporting HA embolization focuses on stabilizing patients presenting with acute tumoral hemorrhage. Emergency surgery for ruptured HA has a 5–10% mortality rate, but embolization may provide a first step in management to achieve hemodynamic stability before resection.[4] If a ruptured HA is less than 5 cm and remains stable following embolization, a nonoperative approach involving strict radiological follow-up may be possible.[21,22] Stoot et al. reported their experience utilizing selective embolization for 11 patients with ruptured HA. The first two patients underwent elective resection following embolization but after histopathological exam revealed complete necrosis. The remaining patients simply received frequent follow-up imaging, and resection was avoided.[23] Indications for HAE for the treatment of HA has expanded in recent years to include nonemergent intratumoral bleeding and as a bridge to resection by reducing tumor size and hemorrhagic potential before surgery.[5,6] Some studies, including those in the current review, have taken HAE a step further as a possible alternative to resection.

Elective Embolization

Karkar et al.[18] reported 100 HA in 52 patients who underwent resection, embolization, or observation. Of the 100 lesions, 37 HA in 13 patients were treated by embolization, with radiologic "suspicion of malignancy" being the most common indication. Of the 37 embolized tumors, only 3 (8.1%) displayed persistent disease following initial treatment, and all were successfully managed with reintervention. Deodhar et al. presented their preliminary experience using bland embolization for the treatment of 17 lesions in 8 patients.[16] Only one patient was experiencing active bleeding at the time of embolization. The authors reported a 100% technical success rate, with no growth in any lesion observed after a median follow-up of 24 (range 10–40) months. One 8.7-$\times$ 11.5-cm lesion was eventually resected due to persistent size. In a smaller case report, Erdogan et al.[5] described five patients with HA, two of which were treated with elective HAE to reduce tumor size. No complications were reported and no repeat procedures were needed. Similarly, Kobayashi et al.[15] reported two HA patients treated with elective embolization. The first had adenomatosis and had the largest lesion embolized. At the time of death 2 years later from heart failure, none of the lesions showed intratumoral hemorrhage or any increase in size. The second patient was a male with hepatic adenomatosis related to GSD-Ia. One year after embolization, none of the masses had increased in size or developed hemorrhage. Although these reports are all retrospective and include carefully selected patients, the promising outcomes warrant further discussion regarding elective embolization for treatment and mass reduction in hemodynamically stable patients.

Elective RFA

Unlike embolization, ablation often is categorized as a curative treatment, rather than a palliative measure. RFA and other ablation techniques have been well-described for small, unresectable hepatic tumors. Whether as an isolated percutaneous therapy for a single lesion or as an intraoperative adjunct to a resection, the technique has been proven safe and effective. The success of ablative therapies for hepatic malignancy has led to its possible use for HA. Ablation may be used as a complement to surgical resection for adenomatosis and as an option for small unresectable HA.[17,24] RFA also has been reported as a treatment option to impede HA growth in patients who desire pregnancy or cannot discontinue hormonal therapy. Furthermore, several case reports describe the use of RFA as an alternative to surgery. For example, some patients especially concerned about aesthetics and invasiveness

may prefer RFA if their disease is deemed amenable.[10,11] In some cases, resection has been avoided with elective up front locoregional treatment, preventing the potential risk of morbidity and mortality associated with surgery, at least in the short-term data presented in these series.

To justify replacement of elective surgery, RFA must be able to demonstrate comparable safety and efficacy. Rhim et al. reported their experience with RFA for ten patients with asymptomatic HA. The patients included in the study chose to undergo RFA rather than traditional surveillance or surgical resection. However, it should be noted that all patients were asymptomatic, with biopsy-proven adenomas less than 5 cm, so surgical resection would not typically be offered to these patients. The authors reported that following ablation, none showed local tumor progression or new recurrence within a mean follow-up period of 17.5 months.[8] In perhaps the largest study reporting RFA for the management of HA, van Vledder et al.[17] treated 18 patients with 45 lesions. The median size of treated lesions was 3.0 cm, and repeat procedures were required in 12 of 45 (27%) attempted ablations. This study is the only one in the current review that had any complications, although neither complication was directly related to RFA. One patient suffered cerebral ischemia secondary to severe intraoperative bleeding; however, she was undergoing concurrent right posterior segmentectomy for one lesion in addition to RFA of two other lesions. Another patient underwent concomitant percutaneous ethanol injection of one lesion and RFA of a second and developed a hepatic abscess at the ethanol site. In one smaller case report, Atwell et al. described the use of percutaneous RFA to treat three patients with HA.[13] The authors reported complete success with no repeat procedures or complications. All lesions demonstrated reduction in tumor size with no evidence of recurrent or residual adenoma. Fujita et al. also treated three HA patients with RFA, but they used an ultrasound-guided technique in combination with lobectomy for multifocal lesions.[14] Seven of the 24 lesions were treated with RFA, and one required repeat ablation, which was successfully performed percutaneously.

Radiofrequency ablation may have a valuable role as an adjunct to resection for multifocal HA and in small, unresectable HA (Table 2). Despite the limited evidence for its use, some consider RFA a viable alternative to elective hepatic resection or watchful waiting for small HA. However, the studies supporting this argument generally include the treatment of tumors less than 5 cm. Common practice is to initiate surveillance for such small tumors, saving intervention for tumors greater than 5 cm. To suggest favoring utilization of elective ablation for tumors under 5 cm would alter the current approach and common criteria for HA management without sufficient data. Until RFA can be compared directly to resection in a randomized setting, it is unlikely to replace resection in common practice. However, if the early findings reported are trusted, the effectiveness of these less invasive modalities provides a logic and potential proposal to further examine their role in select tumors under 5 cm. The patients best served by these early findings are those with 2- to 5-cm adenomas, either growing or not regressing, due to their low malignant risk. In select cases, those patients may be reasonably offered locoregional treatment.

Limitations

This review is subject to several limitations. A selection bias is inherent to the nature of small series and case reports. The patients undergoing elective embolization or ablation were carefully chosen by physicians familiar with the procedures. None of the included studies randomized patients into separate treatment groups. Furthermore, a degree of publication bias is expected to influence results, whereas interest in these approaches remains limited. The "success rate" for the procedures reported among the studies is largely subjective, referring to the technical success of the procedure itself rather than patient outcomes. No standard criteria, such as mRECIST, were used across all studies to indicate effectiveness. For example, a technically successful procedure may still require repeat treatment if a tumor shows persistence at a later date. Additionally, the mean follow-up time of 36 months is not

TABLE 2 Potential indications for locoregional techniques in the management of hepatic adenoma

Clinical (diagnostically driven)	Personal (patient preference)
As a complement to surgical resection in patients with adenomatosis	To prevent further tumor growth in patients who desire pregnancy, or cannot cease OCP use
Anatomically unresectable tumors	Patient prefers non-surgical treatment for aesthetic reasons
Emergent intervention to stop hemorrhage	Patient is a poor surgical candidate or strongly wants to avoid risk of surgical morbidity and mortality

OCP oral contraceptive pill

long enough to assess properly the effectiveness, because malignant conversion could take place beyond that point.

CONCLUSIONS

Hepatic adenomas are a rare and benign disease primarily affecting a young and otherwise healthy patient population, but the risk of hemorrhage and malignant transformation makes identification and treatment crucial. Any patient presenting with an HA-associated hemorrhage or rupture should be treated emergently with hepatic artery embolization to stabilize the patient, and resection should be strongly considered. If embolization is not readily available, resection or packing at laparotomy must be pursued in the hemodynamically unstable patient. Unresectable tumors may be treated with HAE or ablation. The use of such locoregional therapy treatments as an alternative to standard management remains limited to small institutional series and case reports. The patients in this review were carefully selected for these treatments, and exhibited acceptable outcomes, with low rates of repeat procedures and complications. Although surgical resection should remain standard of care, this systematic review warrants further discussion and broader consideration for the treatment of HA.

APPENDIX 1

PubMed search query: (“adenoma”[All Fields] AND (“hepatic”[All Fields] OR “liver”[All Fields] OR “hepatocellular”[All Fields] OR “hepatobiliary”[All Fields])) AND (“ablation”[All Fields] OR “embolization”[All Fields] OR ((“regional”[All Fields] OR “local”[All Fields]) AND (“therapies”[All Fields] OR “therapy”[All Fields])) OR “MWA”[All Fields] OR “RFA”[All Fields] OR “IRE”[All Fields] OR “HAE”[All Fields]) AND English[lang].

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