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Is there a role for perfusion imaging in assessing treatment response following ablative therapy of small renal masses—A systematic review

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ABSTRACT

Aims: Ablation therapies are an innovative nephron-sparing alternative to radical nephrectomy for early stage renal cancers, although determination of treatment success is challenging. We aimed to undertake a systematic review of the literature to determine whether assessment of tumour perfusion may improve response assessment or alter clinical management when compared to standard imaging.

Material and Methods: Two radiologists performed independent primary literature searches for perfusion imaging in response assessment following ablative therapies (radiofrequency ablation and cryotherapy) focused on renal tumours.

Results: 5 of 795 articles were eligible, totaling 110 patients. The study designs were heterogeneous with different imaging techniques, perfusion calculations, reference standard and follow-up periods. All studies found lower perfusion following treatment, with a return of 'high grade' perfusion in the 7/110 patients with residual or recurrent tumour. One study found perfusion curves were different between successfully ablated regions and residual tumour.

Conclusions: Studies were limited by small sample size and heterogeneous methodology. No studies have investigated the impact of perfusion imaging on management. This review highlights the current lack of evidence for perfusion imaging in response assessment following renal ablation, however it suggests that there may be a future role. Further prospective research is required to address this.

1. Introduction

In 2014, there were 12,523 new cases of renal cancer in the UK [1], a number increased by 78% since the 1990s [1]. This can be partly attributed to the increased use of cross-sectional imaging and the consequent incidental finding of small, localised renal masses. As incidental small renal masses have been shown to be generally of lower grade and associated with longer disease-free survival than their symptomatic counterparts [2], nephron-sparing treatments have become preferable to conserve renal function. The surgical gold-standard is now considered to be partial nephrectomy (PN) [3].

An alternative to PN is ablative therapy either using high (radiofrequency ablation, RFA; microwave ablation) or low temperatures (cryotherapy). These techniques are particularly suited to patients with co-morbidities leading to high surgical or anaesthetic risks, poor renal function or a solitary kidney. Comparing percutaneous RFA to PN of small renal masses, RFA has been shown to be associated with less blood loss, smaller post-procedure drop in renal function and shorter length of hospital stay [4–6]. Medium term outcomes are also comparable with no statistical difference in 5 year tumour-related survival or local recurrence [5–8].

The challenge with ablative therapies is determining whether a treatment is successful or not early in the course of treatment. Unlike surgery where pathological assessment of resection margins is possible, determination of complete ablation is more challenging. Early detection of persistent or recurrent tumour will change future management, particularly as the evidence for repeated, invasive surveillance biopsy is inconclusive [9]. Current practice is for initial cross-sectional imaging to be performed typically within 3 months post-procedure, and 3–6 monthly thereafter, the timing varying depending on institutional practice. Ablation is deemed successful if CT shows a hypoattenuating ablation zone with absence of contrast enhancement [10].

Features of persistent tumour that have been described include irregular, nodular enhancement > 10 Hounsfield Units (HU) within the

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ablated area [10]. Whilst contrast-enhancement gives an indication of overall tissue contrast uptake (combination of both intra- and extra-vascular compartments), it is affected by contrast dose, administration rate and cardiac output [11]. Whilst the same is true of quantitative perfusion measurements the effects of these variables can be controlled and mitigated by longer imaging acquisition times and arterial input measurements [12]. It remains unclear whether measuring perfusion is advantageous over qualitative assessment and whether it has any impact on subsequent management. Thus we performed a systematic review of the available medical literature, focusing on whether perfusion imaging has a role as a response biomarker in the assessment of ablation therapies and whether perfusion imaging impacts on subsequent management.

2. Materials and methods

2.1. Data sources and search strategy

We identified primary studies investigating perfusion imaging after ablation of small renal masses from the PubMED database. We included both cryoablation and radiofrequency ablation, with post-procedural perfusion-CT or perfusion-MR or quantitative dual-energy CT.

The following combinations of search terms were applied to identify relevant studies:

(“kidney” OR “renal”) AND (“tumour” OR “tumor” OR “carcinoma” OR “lesion” OR “mass” OR “cancer”) AND (“RFA” OR “radiofrequency” OR “radio frequency” OR “cryotherapy” OR “cryotherapy” OR “cryoablation” OR “ablation” OR “ablative” OR “locoregional therapy”) AND (“CT” OR “MRI” OR “perfusion” OR “dual energy” OR "dual-energy" OR “response” OR “dynamic contrast enhanced CT “OR “dynamic contrast enhanced MRI “OR “DCE-CT” OR “DCE-MRI” OR “quantitative" OR “ASL” OR “arterial spin”).

Results were limited to human studies. No studies were excluded on the basis of language. Relevant systematic reviews were read in full to ensure appropriate studies had not been missed. The search was performed independently by 2 radiologists with any disagreements resolved by consensus.

2.2. Selection criteria

Electronic abstracts of identified studies were read and the following exclusion criteria applied: case reports, narrative reviews, letters/correspondence and conference abstracts were excluded as these would not contribute sufficient unbiased data able to answer our research question. An excluded study log recorded reasons for exclusions.

2.3. Data extraction

Data was extracted from the included full text articles and recorded on a database (Excel, Microsoft, Redmond WA, USA). For each article the publication details and primary characteristics (number of patients, age, size and histology of lesions, ablative technique used, imaging follow-up protocol, summary of findings) was recorded.

2.4. Meta-analysis

Whilst the intention was to perform a meta-analysis on the included data, this was precluded as only a small number of studies have been published with none sharing similar methodology.

3. Results

PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for transparent reporting of systematic reviews were followed (Fig. 1).

3.1. Eligible studies

The initial search performed on 12 February 2018 yielded 795 articles. 724 articles were excluded following evaluation of abstracts. The remaining 71 articles were retrieved in full text and eventually 5/71 (7.0%) studies were included in the systematic review [13–17]. Of these, two studies investigated perfusion-MR following RFA [13,17] and one study each investigated perfusion-MR following cryotherapy [14], perfusion-CT following cryoablation [15], and dual-energy CT after RFA [16].

3.2. Patient population

Characteristics for the included studies are listed in Table 1. 110 patients were included with an individual study range of 10 to 47 patients. The patient age and renal mass sizes were reported differently between studies (range versus standard deviation). 4 studies were limited to RCC; one study included RCC and angiomyolipomata. 4 studies were prospective; 1 was retrospective. 4 studies were European in origin (Germany, Italy, 2 from UK); 1 was Korean. 7/110 patients had residual disease or recurrence following ablation.

3.3. Reported results

With the limited published evidence and varied methodologies in each of the five included papers, the reported results are summarised in Table 2 and described below.

3.4. Changes in perfusion with therapy

Boss et al. [13] compared perfusion-MR (both arterial-spin labeling and dynamic contrast enhanced MR) with T1W-gadolinium enhanced MR. Studies were performed before, 1 day and 6 weeks after MR-guided percutaneous RFA or RCCs. Prior to ablation, RCCs demonstrated “heterogeneous perfusion with zones of cystic tissue necrosis completely lacking perfusion” with a mean tumour perfusion rate of 167 ± 81 $\text{ml.100g}^{-1}.\text{min}^{-1}$. On the Day 1 imaging, the mean reduction was 73 ± 11%. In successful cases, the ablation zones demonstrated further decrease in perfusion between Day 1 and 6 weeks. The mean overall decrease from pre-treatment studies was 84 ± 14%. Wah et al. [17] also performed DCE-MRI before and 1 month after percutaneous RFA of RCCs. They found perfusion decreased significantly within the ablation zone. Interestingly, the degree of pre-ablation perfusion was correlated with the time taken for complete ablation.

Chapman et al. [14] performed DCE-MRI before and 1 month after cryoablation of RCCs in 18 patients. A surrogate measure of perfusion was calculated and then comparisons were made between the signal of the tumour, renal cortex and ablated area. Prior to treatment, mean perfusion within the tumour was 98.0 $\text{ml.100ml}^{-1}.\text{min}^{-1}$. On follow-up imaging, mean perfusion ablation zone perfusion was 11.6 $\text{ml.100ml}^{-1}.\text{min}^{-1}$. This is a decrease of 88.2% ($P = < 0.001$). Only a single follow-up scan was performed on each patient.

Park et al. [16] used iodine-only images from dual-energy CT to quantify iodine-uptake and therefore to infer perfusion following RFA. No perfusion imaging was performed before treatment. Acquisitions were taken in the pre-contrast, corticomedullary and late nephrogenic phases. In successfully treated lesions, iodine uptake peaked in the late nephrogenic phase (mean increase 12.1 ± 11.7 HU). Statistical analysis was not performed.

Squillaci et al. [15] performed qualitative Perfusion-CT 6–8 months after laparoscopic cryoablation of small renal masses. No pre-therapy perfusion-CT imaging was performed. Perfusion curves for successfully treated ablation areas showed more gradual wash-in, lower peak amplitude, and slower washout compared with normal renal cortex.