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Review article

Radiofrequency thermal ablation of renal graft neoplasms: A literature review

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ABSTRACT

Neoplasms occurring in renal grafts represent a relatively novel and rare condition, whose treatment has not been standardized yet. Radiofrequency thermal ablation (RFA) of renal graft neoplasms is a nephron-sparing treatment, reported to be safe and effective. However, even in the RFA field, there is no procedural standardization. In this review of the literature, mostly composed by case reports and case series, we aim to assess efficacy and complication rates of RFA in the treatment of kidney graft neoplasms, and summarize the various procedural protocols found in the literature, using an easy-to-read point format. We performed a literature search in PubMed/MEDLINE with an overall description of 66 renal graft lesion treated with RFA, with a mean follow-up of 16.3 months (range 3–54.3). Technical success was achieved in all cases, with only one recurrence reported (1/66; 1.5%), occurring at 6-months follow-up. Complications occurred in 11 (11/66; 16.7%) patients. Based on literature review, RFA of renal graft neoplasms seems to be a feasible, safe, and effective treatment.

Contents

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1. Introduction

Transplant recipients are at increased risk of cancer: in post-transplant patients, renal cell carcinoma (RCC) of the native kidneys occurs more frequently than in the general population. However, RCC arising in a transplanted kidney is extremely rare and according to the present literature there are no standardized therapeutic approaches [1]. The occurrence of a neoplasm in a graft can be correlated to the presence of various risk factors, such as increased age of the donor, misdiagnosed RCC at the time of graft procurement, chronic post-transplantation immunosuppression, longer life expectancy of both graft and recipient [2–7].

In the past, transplantectomy was the treatment of choice in case of kidney graft neoplasm, with the disadvantage of condemning the patient to life-long haemodialysis [8,9]. In this scenario, nephron-sparing alternatives, with the concomitant aim to eradicate the tumour and grant graft survival, are greatly needed. Partial nephrectomy could be an option, however this isnot always possible, due to patient's comorbidities and consequent higher anaesthesiological risk, presence of a non-naïve hostile abdomen, secondary to adherences and scars, and to patient's unwillingness to undergo major surgery again [10–14].

In non-surgical patients, percutaneous locoregional ablative treatments, such as radiofrequency thermal ablation (RFA), could be offered as an alternative viable therapeutic option.

We conducted a literature review on the safety and efficacy of RFA ablation of renal graft neoplasms, describing and summing-up the evidence-in the literature using an easy-to-read point format that could enhance different specific crucial aspect related to the procedure itself, in terms of indication, procedural technique, and follow-up.

2. Materials and methods

We performed a literature search in PubMed/MEDLINE, for all years, using Medical Subject Headings (MESH) terms, and a combination of the following keywords: radiofrequency, ablation, kidney, renal, transplantation, transplant, graft, allograft, carcinoma, neoplasm.

We retrieved a total of 188 matching articles, and also used article references to select all other relevant articles. All study designs, including case reports, were deemed eligible for inclusion. Non-English articles, or articles without full-text availability, as well as articles lacking procedural details were excluded.

All article abstracts found were independently analysed by two reviewers (A.P. and F.C.) for appropriateness, applying inclusion and exclusion criteria. A third reviewer (R.I.) coordinated and supervised the review process. All literature data were screened and the following parameters were included: patient age at presentation, graft age, lesion dimensions, imaging technique used, ablation times, follow-up data, response and recurrence rates, and complications. Complications were classified as minor or major, according to the Society of Interventional Radiology (SIR) classification system for complications by outcome: major complications were defined as an event requiring increase in the level of care, a prolonged hospitalization, determining high morbidity or disability, or death; all other events were classified as minor complications [15]. Complications were also graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute [16].

3. Results

3.1. Literature search results

We identified 19 pertinent articles, mostly case reports, depicting at least one case of RFA of a renal graft neoplasm. A total of 66 reported lesions were treated with RFA within the last 16 years [17–35]. In detail, the first US-guided RFA of a kidney graft lesion was reported by Charboneau in 2002. Three articles did not include most of the needed data, giving information mostly on the procedural efficacy; however, due to the rarity of this condition, they were included in this review [24,25,32]. One other article, including 5 patients, had aggregate data [28]. The full set of acquired and screened literature data is shown in Table 1. Mean patient age was 58.1 years (range 43–77), whereas mean graft age was 14.4 years (range 0.01–26). Mean tumour size was 21.1 mm (range 7–33).

3.2. Treatment results

Technical success, defined as the ability to complete the treatment cycle and to obtain a complete necrosis of the lesion was obtained in all cases (100%). Mean ablation time was 14 min (range 5–38). During a mean follow-up of 16.3 months (median: 6 months; range 3-62 months), a complete response rate of 98.4% was obtained (62/63), with only 1 recurrence reported 6 months after treatment (1.6%) [20]. No intraprocedural complications were reported; post-procedural complications occurred in 7 cases (11.1%); in detail, Veltri, Cornelis, and Cool reported a total of 4 cases of presumed injury of the genitofemoral nerve or superficial iliopsoas layers, resulting in transitory moderate cruralgia, numbness and neuromuscular deficit of the ipsilateral leg, resolved within 1 year with no treatment or minimal use of anti-inflammatory drugs (SIR class A-B, CTCAE grade 2) [22,26,34]. Furthermore, Cornelis and Christensen reported 2 cases of cutaneous urinary fistula occurred within 4 weeks after treatment, treated with antibiotics and surgical management of the abscess/fistula (SIR class C-D, CTCAE grade 3) [26,30]. The last complication was represented by post-ablation syndrome, with fever and chills, described by Sanchez et al. (SIR class A-B, CTCAE grade 3) [23].

4. Discussion

Minimally invasive treatments for small renal neoplasms are gaining popularity. The well-established surgical procedures, including open radical or partial nephrectomy and laparoscopic radical nephrectomy, can sometimes be too invasive in patients with a high risk of perioperative morbidity, and even a conservative surgery can impair renal graft function. In selected cases, percutaneous therapies, such as RFA, could be a nephron-sparing alternative to partial nephrectomy, with good early results [36–38].

4.1. Patient evaluation

When dealing with transplanted patients, with a non-naïve abdomen and the additional risk of immunosuppression, full and omni-comprehensive approach to patient's clinical status, comorbidities and compliance levels is mandatory. The choice of the right treatment for each patient should be based on a case-by-case discussion within a multidisciplinary tumour board, composed by all the health professionals involved in the field of kidney care, such as transplant surgeon, urologist, nephrologist, oncologist, diagnostic and interventional radiologist, and pathologist. Treatment choice is mainly based on the tumour size, number and localization of the lesions, potential extra-organ spread, and therefore its disease stage.

Graft neoplasms are usually incidental findings, detected in a non-symptomatic patient, in the first stages of their natural history; less commonly, patients can present with macro- or micro-haematuria, acting as a trigger to further examinations, as also reported by Swords et al. [29].

Minimally invasive percutaneous treatments are usually and worldwide performed -regardless of the organ- on lesions up to 3 cm in size or, with a multiple probe-needles approach or multiple ablative sessions, even in larger lesions [20,22,30,39].

On the contrary, a surgical approach consisting of transplantectomy -once considered the gold-standard treatment for kidney neoplasms, but recently replaced by conservative treatments to avoid dialysis- or

Table 1
Literature evidence on RFA of kidney graft neoplasms.

Author	Cases	Patient age (y)	Graft age (y)	Tumour size (mm)	Tumour position	Imaging guidance	Ablation time (min)	Follow-up (months)	Recurrence	Complications
Charboneau [17]	1	50	26	22	partially exophytic, medial	US[b]	20	14	0	0
Baughman [18]	1	46	19	20	cortical, anterior, interpolar	CT[c]	10	3	0	0
Goeman [19]	1	65	23	20	cortical, medial, upper pole	US	12	6	0	0
Aron [20]	1	53	11	32	partially exophytic, posterior, interpolar	CT	38	6	1	0
Matevossian [21]	1	77	12	17	cortical, upper pole	CT	15	6	0	0
Veltri [22]	3	53.3[a]	6.9[a]	28.3[a]	partially exophytic, lower pole; 2 parenchymal, interpolar	US	13[a]	27.7[a]	0	1
Sanchez [23]	1	65	20	20	cortical, posterior	CEUS[d]	N/A	3	0	1
Elkentaoui [24]	2	N/A	N/A	N/A	N/A	N/A	N/A	6[a]	0	0
Leveridge [25]	3	N/A	N/A	N/A	N/A	US/CT	N/A	N/A	0	0
Cornelis [26]	18	53.7[a]	N/A	19.2[a]	N/A	US/CT	N/A	27.7[a]	0	2
Olivani [27]	1	43	11	12	cortical	US	5	3	0	0
Végső [28]	5	N/A	N/A	15–30	4 lower pole, 1 interpolar	CEUS	15–20	N/A	0	0
Swords [29]	1	66	12	7	exophytic, anterior	CT	6	3	0	0
Christensen [30]	1	69	0.01	30	cortical, interpolar/upper pole	N/A	10	54	0	1
Guleryuz [32]	11	N/A	N/A	N/A	N/A	US/CT	N/A	N/A	0	0
Cool [34]	12	49.6[a]	13.2[a]	20[a]	3 exophytic, lower pole; 1 parenchymal, lower pole; 4 exophytic, interpolar; 1 parenchymal, interpolar; 3 exophytic, upper pole	US/CT	10[a]	54.3[a]	0	2
Iezzi [35]	3	65.3[a]	18.3[a]	26[a]	1 cortical, interpolar, anterior; 1 partially exophytic, upper pole, posterior; 1 partially exophytic, upper pole, medial	US	12[a]	15[a]	0	0

[a] Mean values.
[b] US = Ultrasound.
[c] CT = Computed Tomography.
[d] CEUS = Contrast-Enhanced Ultrasound.

partial nephrectomy - which better preserves renal function - can be preferred in lesions larger than 3 cm. Surgical options are associated with a better disease-free survival and local tumour progression rates, as already seen in the setting of liver neoplasms, even when compared to combined locoregional treatments, even though comparative prospective studies in this field of interest are difficult to perform, due to the rarity of this pathological condition [9,40–43].

Tumour position has a great importance when performing an ablative treatment: hilar lesions, or tumours near calyceal groups or renal pelvis, are at higher risk of bleeding and of urinary tract damage, whereas exophytic lesions could be located adjacent to bowel loops or to the bladder which could be damaged, even though there are some strategies to avoid damage to these structures; almost all the RFAs described in the literature were performed on cortical or partially exophytic lesions, easily accessible to the RFA probe, even if sometimes close (< 5 mm) to the calyceal system [17–23,27–30,34,35].

The ideal target for a RFA treatment is, therefore, a single, small (<3 cm) intra-cortical lesion, even though consecutive ablation of two or more graft neoplasms in the same patients, in the same session, have been described, as well as ablation of lesions larger than 3 cm [26,28,35].

The vast majority of Authors staged the neoplasm using the native kidney TNM, whereas, Tillou et al. proposed a modified version of this TNM, most suitable to graft lesions, even if the changes regarded only the parameter T3 and T4, which is not usually encountered in kidney graft lesions undergoing RFA treatments, almost always involving T1a lesions (< 4 cm, confined to the kidney) [44].

Furthermore, patients' refusal to surgery or general anaesthesia is becoming more and more frequent nowadays, and the medical community, aware of this necessary shift in clinical practice, is increasingly opening up, when possible, to minimally invasive percutaneous locoregional treatments [30].

4.2. Pre-treatment biopsy

In order to identify the source of the tumour from the recipient or from the donor, all newly discovered solid graft lesions should undergo percutaneous needle core biopsy, to assess the histological type of RCC, and for potential eventual genetical analysis and immunologic human leukocyte antigen typing, in order to identify the source of the tumour from the recipient or from the donor. In case of a donor-originating neoplasm, the donor must be also followed-up, as well as -in case of transplant from deceased donor- all the patients who received organs from him/her. Fluorescence in-situ hybridization (FISH) on the sample obtained from a male patient's graft neoplasm, showing the presence of female sexual chromosomes (XX), allowed Veltri et al. to state that the tumour originated from the female donor [22,45,46]. It is mandatory to underline that some RCCs can arise as a solid component in cystic lesions, identified as grade IV according to the Bosniak classification of cystic lesions [26,47].

4.3. Ablative treatment

Nowadays, a great number of RFA devices are available on the market, with various needle configurations, but even if the treatments are carried out with the same aim, there is often a big variation in procedural protocol in terms of duration, ranging from 6 and 15 min [21,27] and power applied, ablation temperature reached, based on the operator preference and experience and on the characteristics of every lesion. Treatments are mostly performed under CT-guidance, which grants a panoramic visualization of the graft and of the adjacent organs and tissues, or US-guidance, which grants a real-time feedback of the needle trajectory and placement. In our experience, we usually prefer a mixed imaging guidance: with the patient lying on CT table, using the US for needle positioning and potential intraprocedural check, while an enhanced CT examination was performed soon after the treatment to assess results and exclude possible complications. Sanchez et al. reported a case of CEUS-guided RFA, which could be extensively used for diagnosis, treatment guidance and follow-up in patients who cannot undergo CT or MRI [23].

One of the greatest advantages of RFA is the possibility to perform it under conscious sedation, resulting in a good patient collaboration, with a low degree of pain. However, some Authors reported good results for RFA performed under general anaesthesia, partly due to operator

preference, or patient's difficulty to collaborate, partly related to the location of the graft in left or right iliac fossa [17,26].

Although minimally invasive, all RFAs have to be performed under wide-spectrum antibiotic coverage, to minimize infections risks, greatly amplified in immunosuppressed patients.

In case of partly- or mostly-exophytic cortical graft lesions, some complementary treatment strategies could be useful to avoid damage to the adjacent structures: hydro- and/or pneumo-dissection (with saline or dextrose solution, and/or air or carbon dioxide) of the bowel loops or bladder was described by Cool and Cornelis, the first one describing also, for proximal ureter protection, a continuous chilled saline infusion through a nephrostomy catheter. Bladder was also emptied with an urinary catheter [26,34].

Post-RFA needle tract ablation is usually performed to prevent tumour seeding along the needle insertion tract, even extremely rare [17,19,22,48]. However, whenever the tract ablation is not performed, additional attention must be paid to the ablation site and its surrounding tissue, in order to prevent potential malignant cells dissemination [49]. In order to reduce bleeding complications, it is also important to underline the role of coagulative status of every patient undergoing ablative procedures.

4.4. Patient follow-up and post-procedural care

The great majority of the patients were discharged the day after the procedure, and entered a follow-up programme based on serum creatinine values monitoring, and CT, MRI, or CEUS examinations. According to Cool et al., CEUS should be preferred in case of patients with glomerular filtration rate (GFR) < 45 mL/min, for the lower nephrotoxic risk of the US contrast medium [34].

Cornelis et al. defined a complete tumour necrosis as the absence of enhancement in the treated volume, and incomplete ablation or tumour recurrence as the presence of enhancement (>15 Hounsfield Units on a CT scan) at the first follow-up examination, or after an initial negative examination, respectively [26].

There is no consensus in the literature on the usefulness of a post-ablative biopsy. Aron et al. described the importance of post-ablation site biopsy, to be included in the follow-up protocol, to confirm the complete tumour ablation, even in case of reassuring imaging findings. This approach helped them to discover an otherwise undiagnosed 6-months recurrence, that was promptly re-ablated [20]. On the other hand, other authors support the necessity of a strict follow-up and consider a post-ablative biopsy not sufficiently accurate in recurrence detection [22].

One limitation of the paper in the literature on literature on renal graft ablation is that most of the Authors report a shorter-than-1-year follow-up. In detail, the longest reported follow-up periods were of 62 and 54 months, by Veltri and Christensen respectively, without recurrences [22,30]. A mention needs to be made for the case, reported by Goeman et al., of a RCC previously treated with partial nephrectomy, which recurred and was then successfully treated with RFA [19]. Nonetheless, based on these premises, long-term (> 5 years) follow-ups are mandatory to best evaluate the efficacy of ablative treatments, and to perform effective comparisons to surgical treatments.

In terms of graft function, Leveridge et al. reported 1 patient requiring a second renal transplant due to RFA in kidney with already worsening renal function, which further worsened after RFA [25]. Cool et al. also reported 1 patient with pre-existing graft failure that required dialysis 26 days after RFA; it is good to know, however, that there were no significant differences ($p = 0.32$) in the ratio of mean estimated RFA volume and allograft volume in the patients who required dialysis or re-transplant and the patients with preserved renal function [34].

Maintenance of immunosuppressive therapy is mandatory in transplanted patients, even after cancer diagnosis, to avoid graft failure; however, to the best of our knowledge there are no clear recommendations for its management. In detail, Végső et al. reported the conversion of calcineurin-based immunosuppression to proliferation signal inhibitor (Sirolimus, Everolimus) after the RFA, due to their antiproliferative effect [28,50]. On the other side, Tollefson et al. showed, in localized tumours, a low rate of disease progression despite the immunosuppression regimen; therefore, no change in the immunosuppressive therapy is required [51].

4.5. Other percutaneous treatments

Although kidney graft neoplasms are an uncommon condition, report of percutaneous treatments other than RFA have been made. Cryoablation represents, in fact, a good treatment, suitable for transplanted kidney neoplasms, with its safety and efficacy demonstrated by different Authors. Various case report on the safety and efficacy of percutaneous US-guided cryoablation of renal graft neoplasms have been published [52,53]. According to Atwell et al., for tumours smaller than 3 cm, RFA and cryoablation have similar success, as well as complication and recurrence rates, although cryoablation seems to be more useful for peri-hilar tumours. Therefore, RFA should be performed in peripheral lesions smaller than 3 cm, due to its lower cost, whereas cryoablation should be preferred for central tumours >3 cm in size [54].

Chakera et al. reported a case of a 55-mm RCC of a kidney allograft (stage T1b): the patient refused transplantectomy, and the lesion was deemed too large for RFA; the lesion was treated with High-Intensity Focused Ultrasound (HIFU) two times in 4 months. However, due to the presence of a rim of untreated neoplasm, the patient eventually underwent partial nephrectomy: histological analysis showed great amount of necrosis and only 5–10% of viable tumour cells [44].

5. Conclusions

The development of a renal graft neoplasm is a rare, challenging scenario, however, in recent times it has been increasingly discovered as a consequence of better control and longer duration of the graft: surgical nephron-sparing treatments, such as partial nephrectomy, still represents the preferred method in kidney transplant recipients, to avoid total nephrectomy and the following haemodialysis. However, in non-surgical patients, imaging-guided ablative treatment can represent a feasible, safe, and effective second-line treatment, and should be considered as a viable therapeutic option. Still, to date there is only limited experience on the safety and efficacy of RFA, especially in immunosuppressed patients, and there are no randomized studies comparing graft survival rates and patient's disease-free survival of RFA versus nephron-sparing surgery, nor between the various ablative techniques available nowadays.

Compliance with ethical standards

- "This study was not supported by any funding."
- "The authors declare that they have no conflict of interest."
- "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."
- Institutional Review Board (IRB) approval of our study was obtained.
- "Consent for publication was obtained for every individual person's data included in the study."

Declarations of interest

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