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REVIEW

The Role of Focal Approach as Alternative to Nephron-Sparing Surgery in the Treatment of Stage I Cancer in Renal Graft: Results of a Systematic Review

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SUMMARY

In patients with kidney graft neoplasms, the treatment of choice is still represented by surgical approach, mainly based on partial nephrectomy/nephron sparing surgery (NSS). In this oncologic setting, focal treatments (FT) are becoming more and more useful to avoid the risk of dialysis, considering graft viability of utmost importance. There is still little evidence on which is the best FT option in kidney graft neoplasms and on its therapeutic indications. We performed a systematic review to assess the role of FT such as thermal ablation, interventional radiotherapy, electrochemotherapy, and stereotactic body radiotherapy, as alternative to NSS in the treatment of Stage I kidney cancer. We searched PubMed, Scopus, and Web of Science for articles published between 2010 and 2020 focusing on kidney transplant recipients with kidney graft neoplasm who had undergone FT. The review is framed by the population, intervention, control, and outcomes criteria. The studies underlined safety and efficacy of FT, with low morbidity and good graft survival, but none of them provided a direct comparison with graft nephrectomy or NSS. There is still no clear evidence that FTs, and percutaneous ones in particular, are indicated as a standard treatment in kidney graft neoplasms as opposed to total or partial graft nephrectomy.

Keywords: Focal treatment; graft rejection; nephron sparing surgery; renal transplant patients.

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Introduction

The incidence of renal cell carcinoma (RCC) ranges from 0.5% to 1.5% among renal transplant patients[1,2] occurring in the native kidneys or in the allograft. It represents 4.8% of all malignancies in this setting of patients[3] compared to 3% of the general population. Allograft malignancies occur in 0.2-0.34% of renal transplant patients.[2,4,5]

When managing RCC in allograft kidneys, the physician must balance the need for renal preservation with the need of achieving oncologic control. The treatment of choice for RCC in the allograft kidney is surgery, mainly consisting of partial nephrectomy (PN)/nephron sparing surgery (NSS) wherever possible based on tumor and patient characteristics.[1] PN in renal allografts has the advantage of graft preservation with consequential avoidance of hemodialysis.

The increase in the diagnosis of small renal masses discovered incidentally on follow-up imaging led to considering focal and non-surgical treatments such as radiofrequency ablation, cryoablation, microwave ablation, and focal radiotherapy. Ablative therapies, which have been shown to be a safe and effective treatment for small renal masses,[6] are minimally invasive, associated with a low morbidity, and can be performed percutaneously making them well suited for the treatment of RCC in renal allografts. However, little data exist on outcomes after tumor ablation in transplanted kidneys.

The purpose of this systematic review was to define the role of focal approaches such as thermal ablation (TA) (radiofrequency and microwave, cryoablation), interventional radiotherapy (called also brachytherapy), electrochemotherapy, and stereotactic body radiotherapy (ablative radiotherapy), as alternative to nephron-sparing surgery in the treatment of Stage I kidney cancer.

Materials and Methods

A systematic review was carried out and reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement guidelines.[7] We defined a Population, Intervention, Comparator, and Outcome (PICO) model to elaborate the specific elements of the question. Table 1 reports PICO model. The primary outcome was graft rejection survival during follow-up.

Search Strategy

The literature search was performed by querying electronic databases (PubMed, Scopus, and Web of Science) using selected keywords linked through Boolean operator "AND" and "OR" to build specific search strings for each electronic engineer (Table 2). The article search was completed manually by screening references from relevant papers and using the snowball search technique.

Selection Process

After duplicates removal, single citations retrieved were screened, reading title and abstract. We extracted potentially relevant abstracts, full-text articles, and those who met the inclusion criteria and considered them for final analysis. Two researchers performed citation screening independently and disagreement will be resolved by discussion or by querying a third researcher. An internal multidisciplinary expert team decided about their inclusion in the review. Finally, an external committee performed an independent check and the final approval of the review.
The eligibility criteria were:

Inclusion criteria

The following criteria were included in the study:

- Kidney transplant recipients with kidney graft neoplasm

Table 1 PICO model

PICO	Description
Patients	Kidney transplant recipient with kidney graft neoplasm
Intervention	Focal treatment (thermal ablation, radiofrequency, brachytherapy, electrochemotherapy, stereotactic body radiotherapy, and cryoablation)
Comparator	graft nephrectomy
Outcome	Patient overall survival; progression free survival; graft survival; toxicity; and local control
Time frame	2010-2019

PICO: Population, Intervention, Comparator, and Outcome

Table 2 Literature search

Electronic engineer	Search string
PubMed	(("Renal transplant" OR "kidney transplant" OR "kidney transplantation" OR "renal transplantation") AND (metastasis OR metastatic OR metastases OR "cancer" OR neoplasm OR "tumor" OR "cancers" OR "tumors" OR "tumor" OR "tumors" OR neoplasms OR melanoma) AND ("focal treatment" OR thermal ablation OR radiofrequency OR brachytherapy OR electrochemotherapy OR "stereotactic body radiation therapy" OR "stereo body radiotherapy" OR "stereobody radiotherapy" OR "stereotactic radiotherapy"OR SBRT OR cryoablation) Filters: English; 10 years
Web of Science	ALL=(((Renal transplant) OR (kidney transplant) OR (kidney transplantation) OR (renal transplantation)) AND (metastasis OR metastatic OR metastases OR cancer OR neoplasm OR tumor OR cancers OR tumors OR tumor OR tumors OR neoplasms OR melanoma) AND ((focal treatment) OR thermal ablation OR radiofrequency OR brachytherapy OR electrochemotherapy OR (stereotactic body radiation therapy) OR (stereo body radiotherapy) OR (stereobody radiotherapy) OR (stereotactic radiotherapy) OR SBRT OR cryoablation)
Scopus	(("Renal transplant" OR "kidney transplant" OR "kidney transplantation" OR "renal transplantation") AND (metastasis OR metastatic OR metastases OR "cancer" OR neoplasm OR "tumor" OR "cancers" OR "tumors" OR "tumor" OR "tumors" OR neoplasms OR melanoma)) AND ("focal treatment" OR thermal ablation OR radiofrequency OR brachytherapy OR electrochemotherapy OR"stereotactic body radiation therapy" OR "stereo body radiotherapy" OR "stereobody radiotherapy" OR "stereotactic radiotherapy" OR SBRT OR cryoablation) AND (LIMIT-TO (PUBYEAR, 2019) OR LIMIT-TO (PUBYEAR, 2018) OR LIMIT-TO (PUBYEAR, 2017) OR LIMIT-TO (PUBYEAR, 2016) OR LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012) OR LIMIT-TO (PUBYEAR, 2011) OR LIMIT-TO (PUBYEAR, 2010) OR LIMIT-TO (PUBYEAR, 2009)) AND (LIMIT-TO (LANGUAGE, "English")

- Evaluating the use of focal treatment (FT) (TA, radiofrequency, microwave, cryoablation, brachytherapy, electrochemotherapy, and stereotactic body radiotherapy) compared to graft nephrectomy
- Evaluating as an outcome patient overall survival (OS); progression free survival; graft survival; toxicity; and local control
- English language
- Time restriction (2010-2019)
- Original article.

Exclusion criteria

Conference paper, doubled publication, survey, letter, editorial, book chapter, and review were excluded from the study.

Data extraction and synthesis

Data from selected full-text studies were extracted by two independent authors. The collected data, including first author, country, year of publication, study design, number of patients, type of developed cancer, treatment features, and main results, were then entered in an electronic sheet and compared between the two authors. In presence of differences, the authors analyzed the article and discussed divergent points. A narrative description of the results was finally performed and discussed with the multidisciplinary team.

Results

The literature search strategy resulted in 331 single citations. After literature screening, 24 records were identified for full-text evaluation. Out of these, 12 were excluded and the reasons for exclusion are reported in Figure 1. Eventually, 10 full-texts were considered eligible and were included in results analysis. Twelve additional articles were included based on subtract evaluation because they were clearly eligible. The flowchart of the studies selection process is described in Figure 1.

Characteristics of the Included Studies

All selected studies were retrospective case-series, performed between 2011 and 2019 in France, USA, Hun-

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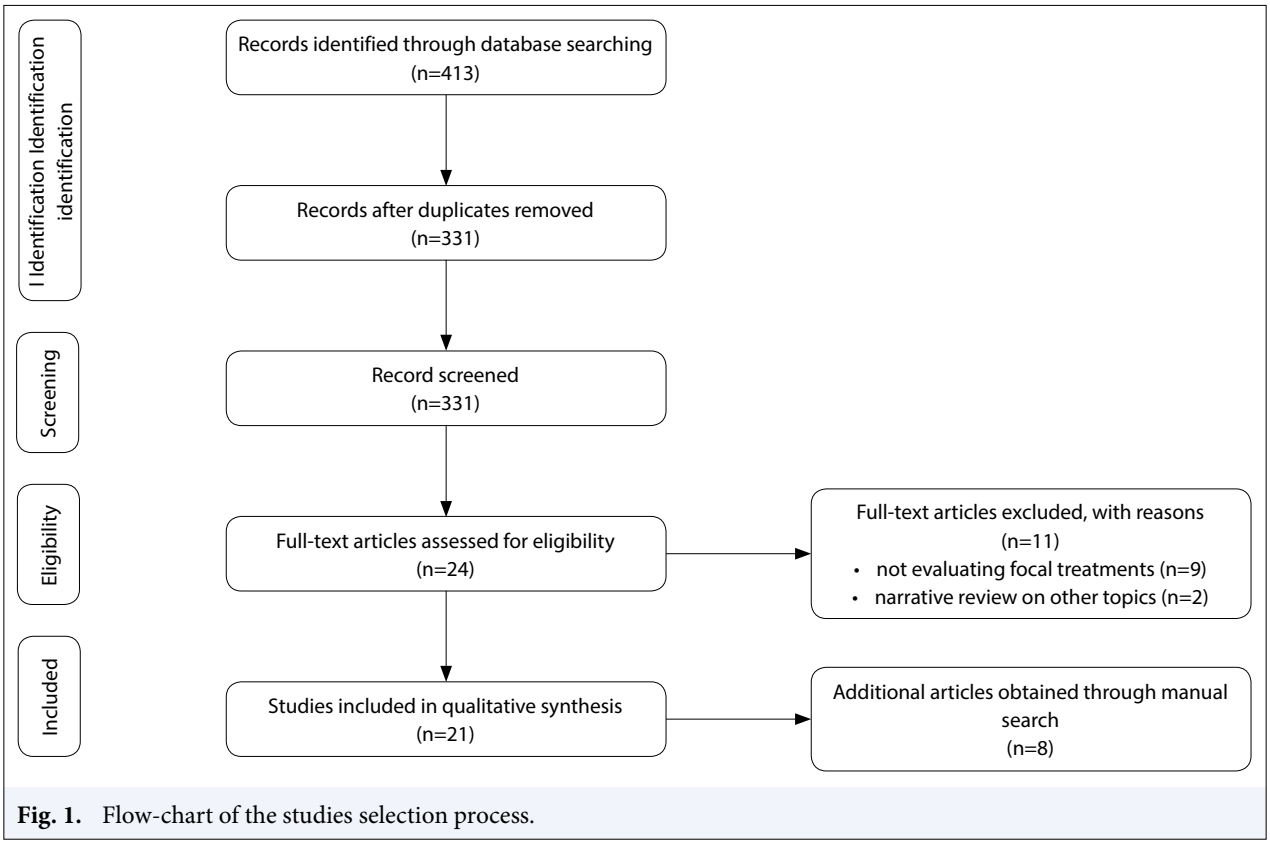

Fig. 1. Flow-chart of the studies selection process.

gary, Canada, Italy, Belgium, Germany, Denmark and Australia. All patients were diagnosed with a kidney graft neoplasm, detected during routine follow-up, and underwent FT (radiofrequency TA, microwave ablation, cryoablation, interventional radiotherapy (IRT, also called brachytherapy), and stereotactic body radiotherapy or partial/total graft nephrectomy. Kidney graft neoplasms approached with FTs were mostly small (<3 cm), unique cortical, or partially exophytic lesions, even though FT of lesions larger than 3cm, as well as of two or more small lesions of the same graft were described. Characteristics of included studies are reported in Table 3.

Twenty studies reported no graft rejection[8-26] while one study showed three graft rejection.[12] Local recurrences were reported in two studies.[17,21]

Christensen and Hansen found a graft neoplasm only 4 days after transplantation, suggesting the donor-origin of the tumor.[11] Pre-treatment biopsy can help to assess the histotype as well as the origin of the neoplasm, as in the case described by Veltri et al., in which Fluorescence *In-Situ* Hybridization performed on the bioptic sample from the graft neoplasm in a male patient revealed the presence of female sexual chromosomes (XX), likely from the female donor.[26,27]

Végső et al.[25] treated nine patients (five RFA and four nephrectomies) and reported a global 1- and 2-years OS of 83.3% and 66.6%, respectively: The five RFA patients were still alive at follow-up, whereas only 25% of nephrectomy patients was alive.

Guleryuz et al.[18] treated 62 patients conservatively including: 48 by PN and 14 by TA. These patients were compared to 30 other patients who were treated by transplant nephrectomy. Nine patients treated by PN had post-operative complications (21%), including four requiring operative intervention (Clavien IIIb). None of the patients treated by TA had complications. None of the 62 patients required post-treatment dialysis, and all transplants were functional 1 month after the treatment. One patient had a recurrence 23 months after treatment with PN. Specific survival was 100% at the time of last follow-up (median time after treatment 37 months) for patients treated by PN or TA.

In addition, there is a great variability between these various studies on FT protocols, even for the same type of FT (e.g., RFA) and for the same specific manufactur-

Table 3 Characteristics of included studies

Author, year (Country)	Title	Objective	Treatment(s)	Main results
Aron, USA (2007) (8)	Percutaneous radiofrequency ablation of tumor in transplanted kidney	Patient and graft survival, treatment efficacy	1 RFA	100% graft and patient survival Viable tumor tissue found at follow-up biopsy, and then retreated with RFA
Baughman et al., USA (2004)[9]	Computerized tomography guided radio frequency ablation of a renal cell carcinoma within a renal allograft	Patient and graft survival, treatment efficacy	1 RFA	100% graft and patient survival No local recurrence
Charboneau et al., USA (2002)[10]	Sonographically guided percutaneous radio frequency ablation of a renal cell carcinoma in a transplanted kidney	Patient and graft survival, treatment efficacy	1 RFA	100% graft and patient survival No local recurrence
Christensen and Hansen, Denmark (2015)[11]	Donor Kidney With Renal Cell Carcinoma Successfully Treated With Radiofrequency Ablation: A Case Report	Patient and graft survival, treatment efficacy	1 RFA	100% graft and patient survival No local recurrence Tumor found 4 days after transplantation
Cool and Kachura, Canada (2017)[12]	Radiofrequency Ablation of T1a Renal Cell Carcinomas within Renal Transplant Allografts: Oncologic Outcomes and Graft Viability	Patient and graft survival, treatment efficacy	10 patients, 12 RFA	No local recurrence at 54.3 months mean follow-up three graft failure, however, with pre-ablation GFR <30 mL/min/1.73 m^2 one death for comorbidities
Cornelis et al., France (2011)[13]	De novo renal tumors arising in kidney transplants: Midterm outcome after percutaneous thermal ablation	Patient and graft survival, treatment efficacy	Radiofrequency ablation (n=19) or cryoablation (n=5)	2/27 DIED None of these patients required dialysis following ablative therapy for their tumors No local recurrence
Elkentaoui et al., France (2010)[14]	Therapeutic management of de novo urological malignancy in renal transplant recipients: the experience of the French Department of Urology and Kidney Transplantation from Bordeaux	Patient and graft survival, treatment efficacy	2 RFA, 1 partial nephrectomy	100% graft and patient survival No local recurrence
Goeman et al., Belgium (2006)[16]	Percutaneous ultrasound-guided radiofrequency ablation of recurrent renal cell carcinoma in renal allograft after partial nephrectomy	Patient and graft survival, treatment efficacy	1 RFA	100% graft and patient survival No local recurrence
Gul et al., 2019 (USA)[17]	Focal Ablative Therapy for Renal Cell Carcinoma in Transplant Allograft Kidneys	Patient and graft survival, treatment efficacy	MWA and IRE	Four patients alive without disease; patient died for stroke and one for infection No patients required dialysis after ablation

Table 3 Cont.

Author, year (Country)	Title	Objective	Treatment(s)	Main results
Guleryuz et al., 2016 (France)[18]	A national study of kidney graft tumor treatments: Toward ablative therapy	Patient and graft survival, treatment efficacy	48 partial nephrectomy and 14 ablative therapy	No graft was lost when a conservative treatment was performed Nine patients treated by PN had post-operative complications (21%), including four requiring operative intervention (Clavien IIIb). None of the patients treated by TA had complications Specific survival was 100% at median FUP of 37 months for patients treated by PN or TA
Iezzi et al., Italy (2019)[15]	Radiofrequency thermal ablation of renal graft neoplasms: Case series and literature review	Patient and graft survival, treatment efficacy	3 RFA	100% alive, mean follow-up 15 months 100% graft survival (mean follow-up 15 months) 100% Complete response
Leveridge et al., Canada (2011) [4]	Renal cell carcinoma in the native and allograft kidneys of renal transplant recipients	Patient survival	Three RFA, two partial nephrectomy, three graft nephrectomy	100% graft and patient survival No local recurrence One patient underwent repeat renal transplantation due to decreased renal function, which preceded but worsened after RFA of the allograft RCC
Matevossian et al., Germany (2008)[19]	Noninvasive therapy of incidental de novo renal cell carcinoma in a kidney allograft 12 years after transplantation: Report of a case and review of literature	Patient and graft survival, treatment efficacy	One RFA	100% graft and patient survival No local recurrence
Olivani et al., Italy (2011)[20]	Percutaneous ultrasound-guided radiofrequency ablation of an allograft renal cell carcinoma: A case report	Patient and graft survival, treatment efficacy	1 RFA	100% graft and patient survival No local recurrence
Ploussard et al., France (2011) [1]	Biopsy-confirmed de novo renal cell carcinoma in renal grafts: A single-centre management experience in a 2396 recipient	Patient and graft survival, treatment efficacy	Two cryoablation, ten nephrectomy/NSS	100% alive (mean FUP 43 months) 100% graft survival one local recurrence in one NSS
Sanchez and Barr, USA (2009)[21]	Contrast-enhanced ultrasound detection and treatment guidance in a renal transplant patient with renal cell carcinoma	Patient and graft survival, treatment efficacy	1 RFA	100% graft and patient survival No local recurrence

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Table 3 Cont.

Author, year (Country)	Title	Objective	Treatment(s)	Main results
Su et al., Australia (2014)[22]	Management of renal masses in transplant allografts at an australian kidney-pancreas transplant unit	Patient and graft survival, treatment efficacy	One RFA, three nephrectomy/NSS	100% alive 100% graft survival (in RFA e NSS) No recurrence
Swords et al., USA (2013)[23]	Treatment options for renal cell carcinoma in renal allografts: A case series from a single institution	Patient and graft survival, treatment efficacy	RFA (two tumors, one patient), three nephrectomy/NSS	100% alive 100% graft survival (RFA and partial nephrectomy)
Tillou et al., France (2012)[24]	De novo kidney graft tumors: Results from a multicentric retrospective national study	Cancer specific survival rates	Nephrectomy (n=35, 44.3%) Radiofrequency (n=5; 6.3%)	5 years cancer specific survival rate was 94%
Végső et al., Hungary (2013)[25]	Detection and management of renal cell carcinoma in the renal allograft	Patient and graft survival, treatment efficacy	Five RFA, four nephrectomy	100% alive RFA; 25% alive nephrectomy (3/4 died: cause of death was tumour progression, pneumonia and sepsis) (mean FUP 22.6 months) 100% graft survival (RFA) 1 y OS: 83.3%; 2y OS 66.6%
Veltri et al., Italy (2009)[26]	Radiofrequency Thermal Ablation of Small Tumors in Transplanted Kidneys: An Evolving Nephron-sparing Option	Patient and graft survival, treatment efficacy	Three RFA	100% graft and patient survival No local recurrence

RFA: Radiofrequency ablation; NSS: Nephron-sparing surgery; MWA: Microwave ablation; TA: Thermal ablation; IRE: Irreversible electroporation; GFR: Glomerular filtration rate; FUP: Follow-up; y: Year; OS: Overall survival; RCC: Renal cell carcinoma

er, in terms of ablation time (reportedly ranging from 6 to 15 min for lesions smaller than 2 cm), temperature, and number of probes.[19,20]

Conservative treatment can be preferred to nephrectomy, when it is feasible, to avoid a return to dialysis: Among conservative treatments, PN is the treatment of choice for small *de novo* kidney tumors. On the other side, FTs, which showed short- and mid-term results similar to nephrectomy, can be considered as alternative therapeutic options, and can be performed during conscious sedation, as opposed to general anesthesia of partial/total graft nephrectomy, reducing the risks for the patient.[18]

Data Synthesis

The studies underlined safety and efficacy of FTs, with low morbidity and good graft survival, but none of them provided a direct comparison with graft NSS. There is still no clear evidence that FTs, and percutaneous ones in particular, are indicated as a standard treatment in kidney graft neoplasms as opposed to total or partial graft nephrectomy.

Discussion

Ultrasound follow-up of kidney grafts is performed routinely and makes easy to diagnose a Stage I renal cancer.[28] Even though PN is considered the treatment of choice in these patients, some of them might not be eligible for surgery for several reasons (comorbidities, tumor site, or histology); in addition, PN would be performed on a non-naive abdominal site which already received graft implant surgery. These patients could likely benefit from a focal approach, which is of great efficacy in small lesions as Stage I neoplasms.[18]

The present systematic review showed that FTs, which demonstrated short- and mid-term results similar to

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PN, can be considered as a good alternative therapeutic option. FTs can be performed during conscious sedation, as opposed to general anesthesia of partial/total graft nephrectomy, reducing the risks for the patient.

In non-transplanted patients, a systematic review and meta-analysis reported that recurrence-free survival and cancer-specific survival were similar between patients treated with PN and TA.[29] These results oppose a previous meta-analysis in which recurrence-free survival was inferior for RFA and cryoablation when compared with PN, although metastasis-free survival was not significantly different among the treatment groups.[30] Klatte et al.[31] performed a systematic review comparing PN and laparoscopic cryoablation and observed a higher risk of recurrence for cryoablation patients, while metastases-free survival was similar. In case of renal transplant patients, the treatment scenario is more complicated. Due to the low incidence of renal graft neoplasms, most studies on the management of renal tumors in transplant allografts come from case reports and short series, and the interpretation of the literature is burdened by the selection bias related to patients' age and comorbidities.[32] These observations suggest that further study is warranted.

When planning a FT of a neoplasm arising from the kidney graft, various elements must be taken in consideration: Among these, the complex net of nerves that crosses and connects different pelvic structures, first of all the genitofemoral nerve which is the one particularly exposed to accidental iatrogenic injury.[33] Age is another important factor that must be taken into account when planning a treatment: An old transplant patient with a renal tumor could be treated with a percutaneous approach even when risk of recurrence is not negligible: This approach, although curative, would offer to this old patient more years of renal function.

The decision regarding allograft mass management was based on the desire to maintain adequate renal function, patient preference and competing health risks, and mass characteristics and site. Kidney graft neoplasms management must be carefully and thoroughly discussed at multidisciplinary renal oncology rounds, considering both the need to be as radical as possible, as well as the need to try to preserve renal function and avoid the risk of dialysis, and also taking into account patient's characteristics and preferences.

Conclusion

Even though there is still no clear evidence that FTs are indicated as a standard treatment in kidney graft neoplasms as opposed to total or partial graft nephrectomy, encouraging data come from the analyzed studies. Randomized studies are needed, as well as studies with larger numbers.

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