INTRODUCTION

Sexual function, including erectile function in men, is increasingly moving into the foreground in the care of patients with renal cell carcinoma (RCC). Historically, metastatic RCC had a rather poor prognosis, due to ineffective therapies, with a median overall survival of approximately 1 year (Motzer et al., 2007). The advent of targeted agents over a decade ago has dramatically improved survival and quality of life (QoL) in patients with advanced disease (Hsieh et al., 2017). Systemic treatment in advanced RCC patients usually comprises multiple sequential treatment lines including antiangiogenic therapy (AAT), most commonly inhibitors of tyrosine kinases (TKI) or the mammalian target of rapamycin (mTOR-inh). In addition, immune checkpoint inhibitors were recently approved for the treatment of metastatic kidney cancer (Hsieh et al., 2017).

The effect of AAT on sexuality and erectile function in patients with RCC has been addressed in prior studies. A recent longitudinal study including both men and women described a decrease in several...
domains of sexuality; however, no association with AAT-related fatigue or biological parameters was found (Denouel et al., 2018). An earlier study also reported a sexual decline, including erectile function, in 38 male patients on AAT for advanced RCC (Bessede et al., 2011).

Sexual function in men can be assessed with the previously validated International Index of Erectile Function (IIEF) (Rosen et al., 2002, 2006). An abridged five-item version of the questionnaire (IIEF-5) is a widely used tool to evaluate erectile function (Rosen et al., 1999). The score has previously been used to evaluate erectile dysfunction (ED) in patients undergoing cancer therapy (Huang et al., 2016; Schoentgen et al., 2019).

The gold standard for the medical treatment of ED is phosphodiesterase-5-inhibitors (PDE-5i). All available PDE-5i drugs yielded a significant increase of erectile function in large randomised studies (Brock et al., 2002; Goldstein et al., 1998, 2012; Hellstrom et al., 2002). However, high medication costs can lead to drug discontinuation in nearly one third of patients (Kim et al., 2014).

In this study, we prospectively addressed sexual activity and the dynamics of erectile function in male patients treated with first-line AAT for advanced RCC at our institution. Moreover, the willingness to use and pay for PDE-5i and the association with erectile function during AAT was assessed.

2 | PATIENTS AND METHODS

2.1 | Patient selection

This study was approved by the Institutional Review Board under the premise to analyse anonymised data. Inclusion criteria comprised the diagnosis of locally advanced or metastatic renal cell carcinoma and treatment initiation with antiangiogenic drugs. In the urologic oncology outpatient clinic of our tertiary care academic centre, 85 patients with metastatic RCC were approached to participate in the study between September 2012 and December 2018. They were asked to complete anonymised questionnaires before initiation of first-line AAT. Assessments were carried out at the beginning (T0) and 12 weeks after the start of systemic treatment (T12). A flow chart displaying the patient selection process is shown in Figure 1.

2.2 | Patient interview items

In order to maintain anonymity, patients received questionnaires to fill out privately after appropriate instruction. Three interview items were included to assess the patients’ subjective perspective on their sexual lives and whether they noticed an improvement or a decline of erectile function at T12. The questionnaire further included social variables, including relationship status and whether regular sexual intercourse (>1x/month) was practised. Additionally, patients were asked whether they desired medical treatment of ED and if they were willing to pay for it out-of-pocket.

To evaluate erectile function, we used the standardised five-item version of the ‘International Index of Erectile Function’ scale (IIEF-5). The complete questionnaire in English, including the IIEF-5 scale and the aforementioned interview items, is provided in Appendix S1. Erectile dysfunction was based on the calculated score and was categorised as follows: no ED (score: 22–25), mild ED (score: 17–21), mild-to-moderate ED (score: 12–16), moderate ED (score: 8–11) and severe ED (score: <8) (Rosen et al., 1999). Following completion of the survey patients were offered personal counselling, in-depth assessment and upon request, medical treatment of erectile dysfunction, in the form of an on-demand treatment with sildenafil, with dose titrations performed depending on patients’ responses. This offer was
possible, as the treating urologic oncologists in our outpatient clinic are urologists with expertise in andrology and sexual medicine.

2.3 | Statistical analysis

All statistical analyses were performed using the R platform v3.5.3. Nonparametric hypothesis testing was performed as data were non-normally distributed. For unpaired data, Fisher’s exact test was used for binary and the Mann–Whitney U test for numeric outcomes. With regard to paired data, the Wilcoxon signed-rank test was performed for numeric and McNemar’s test for binary outcomes. RCC subtypes were divided into clear cell (ccRCC) and nonclear cell RCC (nccRCC). Patients with concurrent ccRCC and nccRCC lesions were counted as nccRCC. To assess a potential correlation between IIEF-5 score variation between T0/T12 and patient age, IIEF-5 values at T0 were subtracted from scores at T12 and the Spearman rank correlation test was carried out. Tests were performed two-sided; statistical significance was defined by a p-value of <.05.

3 | RESULTS

3.1 | Baseline characteristics

Table 1 provides an overview of baseline characteristics of our cohort. 37/85 (43.5%) men completed both T0 and T12 questionnaires and were included in further analysis. The median age of the cohort was 63 years (range: 40–84.2 years). Twenty-nine (78.4%) men were in a steady sexual relationship; 18 (48.6%) patients reported having regular sexual intercourse at T0 and 17 (45.9%) at T12. With respect to tumour subtype, 26/37 (70.3%) had clear cell RCC (ccRCC), 8/37 (21.6%) papillary RCC (pRCC) and 5/37 (13.5%) had other rare RCC variants. However, 2/37 (5.4%) patients displayed both ccRCC and pRCC lesions in their pathological report and were counted as nccRCC variants. Thirty-three (89.2%) patients underwent TKI therapy, while the rest of the group received an mTOR-inhibitor (n = 2, 5.4%) or a TKI/mTOR-inh combination regimen (n = 1, 2.7%) as first-line treatment.

3.2 | Erectile function at T0 and T12

Figure 2 illustrates the distribution of IIEF-5 scores for the two time points of interest. The median IIEF-5 score at baseline was 13 (IQR: 6–20). Twelve weeks into therapy, the median IIEF-5 score significantly decreased to 9 (IQR: 2–16, p < .001). The number of patients in each of the IIEF-5 categories at both time points is listed in Table 2. As the patient age ranged from 40 to 84.2 years, we performed a Spearman rank correlation test to explore a potential correlation between age and variations of erectile function scores between T0 and T12. However, no such correlation was found (Spearman ρ = .11, p = .51). There also was no significant association between IIEF-5 scores at T0/T12 and RCC subtype (p = .97 and p = .72, respectively).

3.3 | Subjective assessment of sexual function

At T0, 21 (56.8%) patients reported to be satisfied with their sexual lives. After 12 weeks, this number was reduced to 16 (43.2%) men (p = .074). For both time points, a satisfactory sexual life was associated with higher IIEF-5 scores (p = .006 and p = .03, respectively). At T12, 4 (10.8%) patients described an improvement of their erectile function, while 28 (75.7%) men reported a deterioration; the remaining 5 (13.5%) patients described neither of both. Patients reporting an improvement of erectile function showed a statistical trend regarding an increase of IIEF-5 scores compared with the rest of the cohort (median score increase: +0.5 vs. −1, p = .078). In patients who reported a subjective decline of erectile function, a nonsignificant decrease of IIEF-5 scores was found with comparison to the other cases (median score decrease: −1.5 vs. −1, p = .27); no significant association between subjective deterioration and sexual satisfaction was found (p = .14). Strong consideration of a PDE-5i therapy (presuming the willingness to pay for medication) was only observed in 1/4 patients with subjective improvement and no significant association was shown (p = 1). Subjective improvement was also not associated with patients’ subjective satisfaction with their sexual lives at T12 (p = .3). Regular sexual intercourse was significantly associated with higher IIEF-5 scores at both time points (p = .001 and p = .002, respectively) and with subjective sexual satisfaction at T0 (p = .02) (Table 3). There was no significant association between IIEF-5 scores and relationship status and no significant association between histological variants (ccRCC vs. nccRCC) and sexual satisfaction at T0 or T12 (p = .49 and p = .74, respectively).

3.4 | Willingness to use and pay for PDE-5i

A total of 21/37 (56.8%) men in our cohort were interested in medical treatment of ED at both time points; 14/21 (66.7%) were
willing or able to pay for medication at T0 and 13/21 (61.9%) at T12. Both T0 and T12 IIEF-5 scores were significantly higher in patients who were willing to pay for PDE-5i (p < .001 and p = .005, respectively, Figure 3). Sexual satisfaction in these patients was significantly higher at both time points (p = .048 and p = .036, respectively).

4 | DISCUSSION

Previous studies have shown that sexuality plays an essential role for all age groups, including the elderly population, and can be considered as a cornerstone of global life satisfaction (Morton, 2017; Skałacka & Gerymski, 2019). Cancer diagnosis and related treatments have a detrimental effect on sexual function (Schover, 2005; Stanton et al., 2018).

To assess this association in patients with kidney cancer, we designed a longitudinal study on sexual function in men on AAT for advanced RCC. Male kidney cancer patients are commonly in their seventh life decade and can therefore be considered sexually active (Bessede et al., 2011; Lindau et al., 2007).

We queried a cohort of patients with a median age of 63 years during first-line antiangiogenic therapy for metastatic kidney cancer. After 12 weeks of treatment, a significant reduction of IIEF-5 scores was observed. Further, subjective sexual satisfaction was associated with IIEF-5 scores and showed a non-significant trend towards decline in the course of treatment. An earlier study in a representative population sample of more than 4,400 men between 30 and 80 years of age reported several variables of sexual health. In the age group of 60–69 years, the prevalence of ED was 34.4%, with approximately 60% of men describing subjective sexual satisfaction (Braun et al., 2000). The prevalence of ED in our cohort was higher with approximately 84% at T0; however, the percentage of subjectively satisfied patients was comparable (56.8%). It is noteworthy that Braun et al. did not use the IIEF score to evaluate ED.

The majority of patients in our study described a deterioration of erectile function after 12 weeks of AAT. In patients with...
subjective decline or improvement of erectile function, accordingly lower and higher median IIEF-5 scores were recorded; however, the results were not statistically significant. Subjective improvement at T12 was rare, occurring in only 4/37 patients. Neither the consideration of PDE-5i therapy nor subjective satisfaction was significantly associated with it. Based on these aspects and the low number of appropriate cases, no conclusive statement can be made on shared features of these individuals. IIEF-5 scores both at therapy start and 12 weeks later were higher in patients who strongly considered the use of PDE-5i. These findings suggest that erectile function has a significant impact on patients' general sexual satisfaction and that patients with better function are more interested in improving their sexual lives even further by using medical therapy. However, despite generally low median IIEF-5 scores, more or less half of the patients at both time points described their sexual lives as satisfactory, highlighting that both concepts are not necessarily related to each other.

So far, only few studies have evaluated sexual function in small cohorts of patients with metastatic RCC. Most recently, Denouel et al. addressed changes in multiple sexual dimensions in both men and women with RCC undergoing first- or second-line AAT and explored the relationship between sexual disorders and biologic parameters, QoL and fatigue. The authors observed a decrease in several areas of sexuality, such as pleasure and desire, in the majority of patients. They could, however, neither find an association with hormonal or inflammatory parameters in the blood nor with fatigue. Erectile function was part of the Changes of Sexual Functioning Questionnaire (CSFQ) used by the authors, but it was not one of the mainly affected domains of sexuality. However, it is important to note that the items of the CSFQ differ from the IIEF questionnaire with regard to erectile function (Denouel et al., 2018).

An earlier study by Bessede et al. also included patients with advanced RCC. Following 4 months of AAT, the authors detected a reduction of several dimensions of sexual function using the IIEF questionnaire. While intensity and quality of sexuality, including erectile function, deteriorated, sexual desire remained high (Bessede et al., 2011). Similarly, Rouanne et al. (2013) reported a decline in sexual function in both men and women after 1 month of AAT for advanced or metastatic cancer, with only one RCC patient included. The findings are in line with our report of decrease of erectile function in patients on first-line AAT for RCC. However, we did not evaluate further domains of sexuality other than erectile function. The median age of participants in previous study cohorts was comparable to our study, with 59 years in the study by Denouel et al. and 58 years in the work by Bessede et al. The male patients in the study by Rouanne et al. had a mean age of 56 years, also comparable to our cohort. The authors reported that age was not associated with a variation of the IIEF score between baseline and 1-month follow-up time point. This is relatively consistent with our study, in which no correlation between erectile function and patient age was found at either time point.

A major aspect, that is still insufficiently elucidated, is the direct effect of antiangiogenic drugs employed in RCC on sexual function. In this regard, mTOR-inh may exert a negative effect on gonadal hormones, as previously suggested in patients following renal transplantation (Huyghe et al., 2007). However, in an earlier study looking into the association between mTOR-inh and erectile function, including 66 male renal transplant recipients, no significant difference in IIEF scores could be found (Lee et al., 2005). In the present study, only three
patients received mTOR-inh, precluding a statistically conclusive attribution of the effects of this substance group. TKIs target the VEGF pathway and earlier studies hypothesised that TKIs could lead to sexual dysfunction by causing an endocrine imbalance (Bessede et al., 2011; Wong et al., 2007). However, studies of imatinib, a TKI inhibiting the platelet-derived growth factor receptor (PDGFR) and used in patients with chronic myeloid leukaemia, have shown a favourable impact on erectile and vascular function. In vitro and animal tests with imatinib led to smooth muscle relaxation via the nitric oxide/guanosine monophosphate pathway in the human tissue (Gur et al., 2010, 2013). These contradicting results with respect to the in vivo impact of AAT in humans, impede to draw causal links between AAT use and ED. More so, as erections are caused and influenced by the complex interplay of neurological, vascular, and psychological factors (Marcon & Stief, 2020).

In this context, cancer-related symptoms, such as pain, fatigue, or altered body image may also negatively influence sexuality. Overall, the role of psychosocial issues in patients with advanced RCC as well as the association with detailed side effect profiles should not be underestimated. While relationship status was not associated with erectile function, it is interesting to note that patients with regular sexual intercourse had better IIEF-5 scores and higher sexual satisfaction at the beginning of the study. This may suggest that regular intercourse and the active engagement in sexuality may benefit erectile function. Affected patients should therefore proactively be offered a comprehensive assessment of sexual function. While men included in the study showed high acceptance of sexual counselling, it should be pointed out that in our practice urologic oncology treatment is delivered by urologists with knowledge of sexual medicine. In oncology clinics, a referral to sexual counselling may be beneficial for affected patients. Sexual disorders in cancer patients can generally be regarded as a combination of biological, psychological, and social factors (Dobkin & Bradley, 1991). Therefore, psycho-oncological referral should be offered early on during oncologic care.

PDE-5i are an established first-line therapy option for patients with ED of different etiologies, with high patient satisfaction rates and good long-term results (Marcon & Stief, 2020). The association between interest in PDE-5i and higher erectile function scores in our study suggests that sexually more active patients aim to reach out for supportive treatment. As a consequence, pro-erectile drugs should be made available early on to patients undergoing AAT. However, in the present study, only 70% of the patients interested in ED treatment were willing to pay for it out-of-pocket. A main concern for patients is the treatment price which is usually not covered by health insurance policies (Kim et al., 2014).

Recent patent expirations of PDE-5i drugs have led to the launch of affordable generics. This enormous cost alleviation has ignited discussions in different countries, whether reimbursement for PDE-5i should be permitted (Hansen et al., 2020). Both price reductions due to upcoming patent expirations and potential reimbursement may increase ED therapy acceptance in affected patients.

Limitations of our study include the large proportion of patients not completing the questionnaire, the missing long-term follow-up as well as the absence of a control arm. This study was focused on male sexuality and in particular erectile function, while female sexual dysfunction on AAT was not contemplated. Anonymisation of patient data prevented assessment of detailed clinicopathologic parameters, influence of biological variables, detailed comorbidities (e.g. by using the Charlson Comorbidity Index, Charlson et al., 1987) and observation of adverse events related to either targeted agents or PDE-5i. A detailed documentation of dosages used after the common starting dose of 50 mg sildenafil was also not carried out, as the focus of this work was put on patients' motivation to use PDE-5i. Another aspect regards the missing long-term follow-up data which, in combination with information on therapy response (e.g. by performing a RECIST-based imaging analysis), could shed light on the association between response and sexual function.

Lastly, the study started before the advent of immune checkpoint inhibitors in the treatment of RCC, a class of agents currently dominating the first-line treatment.

Future studies to assess the impact of checkpoint inhibitors on sexual function are urgently needed. We further believe that the implementation of other IIEF items, apart from erectile function, could shed light on the dynamics of other sexual dimensions and should be integrated into the management of cancer patients. Sexual health and erectile function are relevant to patients starting systemic treatment for advanced RCC. The study taught us that questionnaires are helpful tools to introduce this sensitive issue, but the treating physician should proactively address sexual dysfunction and inform about beneficial therapy options.

5 | CONCLUSION

After 12 weeks of AAT, patients with advanced RCC showed a decline of erectile function scores. With regard to patients' contentment with their sexual lives, the results after 12 weeks trended towards a lower satisfaction. Furthermore, patients with both higher objective and subjective erectile function were more inclined towards medical treatment of erectile dysfunction. The impact of the psychosocial burden in affected patients warrants further elucidation.

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DATA AVAILABILITY STATEMENT
Data available on request from the authors.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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