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ORIGINAL ARTICLE

Adjuvant therapy in renal cell carcinoma: the perspective of urologists

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Abstract

Background Until recently, there was no approved adjuvant therapy (AT) for renal cell carcinoma (RCC) unless sunitinib was approved in the US. We evaluated clinical opinion and estimated use regarding different treatment options and patient selection of AT in RCC patients based on current scientific data and individual experience in Germany.

Methods We conducted an anonymous survey during a national urology conference in 01/2017. Answers of 157 urologists treating RCC patients could be included. Questions were related to practice setting, treatment of RCC, follow-up strategy, physicians' personal opinion and individually different important parameters regarding S-TRAC and ASSURE-trial.

Results 82% were office based. 67% were located in larger cities. 83% reported that nephron-sparing surgery (NSS) was performed in tumors with diameter < 4 cm. Follow-up was done mainly in concordance with guideline recommendations. 68% treated an average of 2.9 patients/year with systemic therapy. Therapy was predominantly advocated using sunitinib (94%). Urologists were informed about S-TRAC and ASSURE-trial. For 47%, reported hazard ratio is the most important parameter to understand trial results followed by overall survival (OS) in 46%, disease-free survival in 38%, and results of other trials in 34%. The most convincing parameter to decide on AT is OS (69%). 62% placed their confidence in ASSURE over STRAC-trial. 44% would use AT for 12 months. Nodal involvement was the most common denominator for use of AT. 82% favor sunitinib as AT.

Conclusions A minority of urologists would use AT and are more confident in ASSURE-trial. Reluctance of prescribing AT mainly is based on lack of OS data and conflicting trial results.

Keywords Renal cell carcinoma · High-risk carcinoma · Adjuvant therapy · Statistical data interpretation · Targeted therapy

Introduction

The incidence of renal cell cancer (RCC) is rising to 15.9 per 100,000 men and women per year. RCC has a mortality of 3.8 per 100,000 patients per year [1]. RCC is mostly diagnosed incidentally within the framework of imaging because of other diseases. Surgical management is the standard treatment for localized or locally advanced RCC. Nephron-sparing surgery (NSS) or radical nephrectomy is the standard of care for localized disease [2]. The prognosis of patients with localized RCC mainly depends on size, stage, grade, nodal and metastatic status. The risk of recurrence after curative therapy can be assessed using validated models like the University of California Los Angeles Integrated Staging System (UISS) [3] and the stage, size, grade, and necrosis (SSIGN) score, presented by Leibovic et al. [4].

Targeted therapies, including tyrosine kinase inhibitors (TKI) and mTOR inhibitors, have been introduced in 2006 and since then became a fundamental cornerstone for the treatment of metastatic RCC. The prognosis for patients with metastatic RCC has improved in the past 12 years, but no curative treatment is currently available and complete tumor eradication of measurable metastases has rarely been reported. Patients classified as high-risk RCC have a likelihood of over 50% for recurrence after complete surgical resection [5]. This is likely due to the growth of microscopic metastases that are present at the time of diagnosis and develop during the perioperative period. The aim of adjuvant therapy is to eradicate these invisible tumors and thus improve disease-free (DFS) and overall survival (OS). Previous adjuvant strategies and trials of interleukin 2, interferon, hormonal therapy, radiotherapy or chemotherapy have not been successful to achieve this [6, 7]. Over

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the last decade, several trials were performed in the adjuvant setting based on the administration of TKI and mTOR inhibitors in patients at high risk of recurrence. Two important trials, STRAC (NCT0037567) [8] and ASSURE trial (NCT003268) [5], were both published in 2016 including 615 and 1943 patients, respectively. STRAC was a placebo-controlled randomized, double-blind, phase 3 trial to evaluate the efficacy and safety of adjuvant sunitinib. ASSURE was a double-blind, placebo-controlled, randomized, phase 3 trial which compared the efficacy and safety of sunitinib or sorafenib in an adjuvant setting. ASSURE and STRAC have fundamentally different results: The primary endpoint of ASSURE did not differ between the groups. Median disease-free survival was 5.8 years (IQR 1.6–8.2) for sunitinib (hazard ratio [HR] 1.02, 97.5% CI 0.85–1.23, $p=0.8038$), 6.1 years (IQR 1.7—not estimable [NE]) for sorafenib (HR 0.97, 97.5% CI 0.80–1.17, $p=0.7184$), and 6.6 years (IQR 1.5-NE) for placebo. In the STRAC trial, the median duration of disease-free survival was 6.8 years (95% confidence interval [CI] 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI 3.8–6.6) in the placebo group (hazard ratio 0.76; 95% CI 0.59–0.98; $p=0.03$). At the moment, there is no recommendation for adjuvant therapy in urologic guidelines [2, 9]. In the US, the US Food and Drug Administration (FDA) has approved sunitinib for AT of RCC at high risk of recurrence following nephrectomy. Approval is pending in the European Union (EU) [10].

We want to evaluate the clinical opinion and the estimated use regarding different treatment options and patient selection of AT in patients with RCC based on current scientific data, especially STRAC and ASSURE, and individual experience.

Materials and methods

A questionnaire with 20 questions was designed for the target group of urologists. Questions were related to practice setting, hospital or office based and population of their working area, surgical and medical treatment of RCC including different surgical options regarding tumor size and drug management in the adjuvant and metastatic setting as well as follow-up modalities (see att. 1).

The written survey was conducted anonymously during a national conference of urology in January 2017. Answers of 157 urologists from Germany, Austria and Switzerland treating and following patients with RCC could be included in the analysis. Statistical analysis was performed with Microsoft Excel 2016 and IBM SPSS Statistics (version 25, IBM).

Results

18% (28/157) of the urologists' work in a hospital and 82% (129/157) are office based. 67% (105/157) reside in a city with 10,000–100,000 inhabitants, 29% (46/157) of them in a city with more than 100,000 inhabitants and the minority with 4% (6/157) in a small town with less than 10,000 people. 95% (149/157) of the urologists do offer medical care to patients with RCC.

Nephron-sparing surgery (NSS) in tumors smaller than 4 cm was considered by 83% of the urologists. In tumors with a diameter of 4–7 cm, 51% would prefer NSS and 49% radical nephrectomy (Nx). Renal masses larger than 7 cm are treated with NSS in 12%. 6% did not specify their preferred surgical management.

Surveillance mainly consisted of chest X-ray, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, chest CT and abdominal ultrasound at different intervals. 2% of the responding doctors did not provide any follow-up and 16% propose variable intervals with different imaging modalities depending on the patient's individual risk. The majority 65% (102/157) conducted an abdominal ultrasound every 3 months, 11% (17/157) did it every 6 months. MRI or CT of the abdomen was done by 8% in a 3-month and by 43% of the urologists in a 6-month interval. 25% of them offer it after 12 months to the patient. Chest CT was done in 8 patients after 3 months, 40 patients after 6 months and 47 after 1 year. 35 patients got an X-ray done for follow-up within the first 12 months.

69% (108/157) of the responders treated patients with systemic therapy with a mean of 2.9 patients per year. 94% (102/108) used sunitinib as a therapeutic option in metastatic RCC. 48% reported to prescribe pazopanib, 25% sorafenib, 21% of immunotherapy (PD-1), 12% everolimus and 8% temsirolimus (Fig. 1).

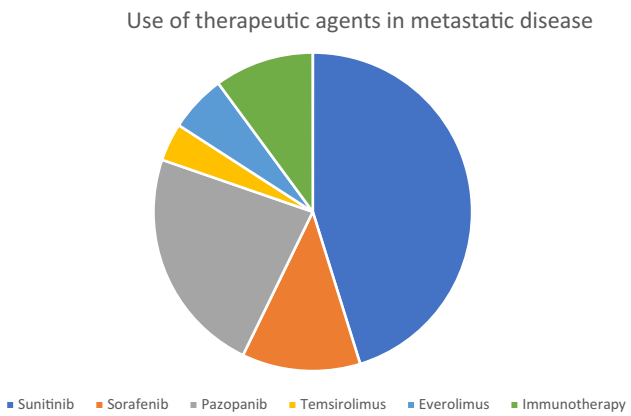

Fig. 1 Use of therapeutic agents in metastatic disease

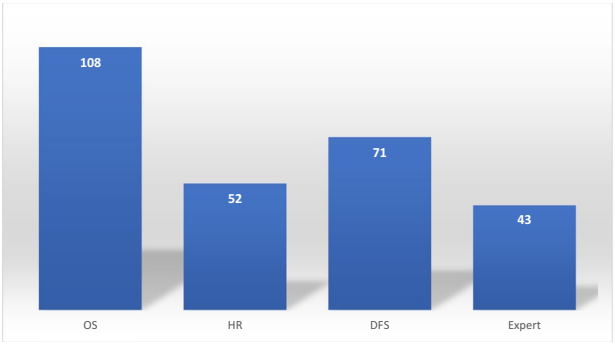

Fig. 2 Most convincing statistical parameter for trial assessment. Decision-making in favor of adjuvant treatment

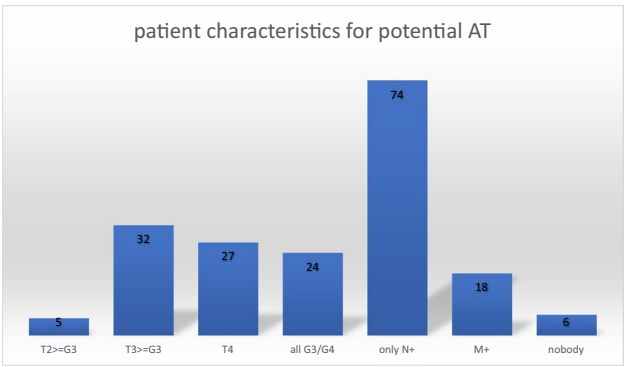

Fig. 3 Patient characteristics for potential adjuvant therapy

38% (60/157) of the urologists reported that DFS is a sufficient criterion for the assessment of AT. For 46%, the OS is the most relevant parameter for evaluation, 47% (73/157) considered HR. The knowledge of other studies regarding AT is important for 34% (53/157). Decision-making in favor of AT was chosen to be most relevant by 69% (108/157) for OS followed by DFS in 71 cases, HR in 52 and expert opinions in 43. 62% (95/157) trusted the results of ASSURE to be used as the basis for their treatment decision and 38% (58/157) the STRAC trial (Fig. 2).

44% (69/157) would treat their patients with AT with a mean duration of 11.9 months. The majority of the doctors reported to already treat patients with positive lymph nodes (74/157) with AT. 32/157 would treat patients with a T3 RCC and at least grade 3 tumor. Detailed results are shown in Fig. 3. Urologists claim to see 2.6 patients per year with a potential indication of AT. 76% (119/157) would use sunitinib for AT followed by pazopanib (24/157), sorafenib (15/157) and immunotherapy (8/157). 62% (97/157) answered that the adjuvant therapeutic option will influence their therapeutic management regarding first-line therapy in mRCC.

Discussion

Two large phase 3 trials on adjuvant therapy based on TKI therapy were published in 2016. Prior to these, several trials using different therapeutic approaches in the adjuvant setting could not prove a benefit of systemic therapy over placebo [11]. As of today, no guideline recommendation for treatment in the adjuvant setting for RCC at high risk of recurrence exists. AT still is challenged based on conflicting data of ASSURE and STRAC [12]. The perception and interpretation of these results was the subject of this poll in Germany. There is currently a negative trend towards the use of AT (56%), but it is not significant. As shown, there is uncertainty regarding patient selection and choosing efficient and valuable therapy. The variety of inclusion criteria and implementation is also a problem in the TKI trials: ASSURE included all histological subgroups of RCC and STRAC included only clear cell RCC. ASSURE allowed for a higher dose reduction than STRAC (sunitinib 25 mg versus 37.5 mg). Furthermore, the assessment was investigator assessed in ASSURE and centralized in STRAC. All these biases eventually explain different outcomes in the trials. Subgroup analysis of the ASSURE trial also revealed that there is no difference of treatment with sunitinib or sorafenib concerning placebo in spite of different patient populations.

Urologists stated that OS is the most important endpoint for decision-making regarding AT. In STRAC, the OS was a secondary endpoint and was not mature in 2016 because median OS could not be reached. OS in ASSURE trial was reported and did not differ significantly between the groups with a HR of 1.17 for sunitinib versus placebo and HR 0.98 for sorafenib versus placebo [5]. HR and OS were important parameters for urologists to compare different trials. Including the attitude of the doctors it is not surprising that the majority reported to trust more the results of ASSURE and the minority would treat patients in an adjuvant setting.

At the moment, sunitinib is the most acceptable therapy for urologists. Probably this effect can be explained by the common use in metastatic RCC and a more renowned management of side effects compared to other therapeutics as well as the best evidence of published trials. The PROTECT trial was not a subject of this survey because of missing data at the time of data collection [13]. Battle et al. published a survey with 450 RCC patients in the US about their attitude towards AT [14]: patients are willing to use AT based on benefits in OS as well as DFS neglecting toxicity. The high willingness of patients to use AT is waived until now. Maybe this knowledge will influence the decision towards the management of patients with high-risk RCC.

Strong evidence based on study experience and randomized trials for the incorporation of AT in high-risk RCC

is lacking [15]. Currently, results of the PROTECT trial—which compared pazopanib versus placebo in AT—and the ATLAS trial—axitinib versus placebo in an adjuvant setting—are available [13, 16]: ATLAS did not reach the OS as its primary endpoint but there seems to be an improvement of DFS per investigator for high-risk RCC patients. PROTECT trial could not demonstrate a DFS improvement of pazopanib versus placebo. Until now, multiple targeted therapies were examined but only one is approved for use in the US [10]. Results of ongoing and future trials using immunotherapy and targeted agents as well as genetic or molecular based prognostic models are needed to specify who may benefit from AT. If an evidence-based recommendation would be provided based on specified criteria for whom which agent should be used depending on the individual patient risk, the reluctance of the clinicians to use AT might be reduced.

This study had several limitations. The included data were gathered from 157 urologists working in Germany, Austria or Switzerland. With an average of 2.9 mRCC patients treated per year per urologist, we also included so-called low-volume urologists. However, RCC, especially metastatic RCC, is a rare disease in Europe; the number of treated patients with systemic therapy per urologist represents a "real-world" setting. We asked specialists for RCC as well as office-based urologists who treat mRCC patients but not exclusively. We did not specifically analyze differences between these groups of physicians.

Conclusion

Generally, acceptance to use AT is low amongst urologists. OS and HR are considered the most important statistical outcome parameter which physicians rely on to compare clinical trials. 62% of clinicians trust the ASSURE over the STRAC trial. 44% would use AT in high-risk RCC patients for a median duration of 12 months and would mostly use sunitinib. AT would influence the choice of first-line therapy. Because of the lack of evidence-based results, further studies to identify efficient and safe AT drugs are warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This manuscript does not contain any studies with human participants or animals performed by any of the authors.

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