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Focal Therapy for Renal Cancer: Comparative Trends in the USA and Germany from 2006 to 2020 and Analysis of the German Health Care Landscape

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Keywords
Focal therapy · Renal cell carcinoma · Population-based study · Trends · Ablation techniques · Kidney

Abstract
Introduction: The aim of the study was to investigate trends of FT for in-patient treatment of renal RCC in the USA and Germany. ***Methods:*** We analyzed the SEER database for the USA and the nationwide German hospital billing database each from 2006 to 2019 for a RCC diagnosis in combination with FT, radical nephrectomy, and partial nephrectomy. FT was defined as radiofrequency ablation (RFA) or cryotherapy. Linear regression analysis was performed to detect changes over time. ***Results:*** For the USA, we included 7,318 FT cases. The share of FT increased from 2.4% in 2006 to 6.4% in 2019 ($p < 0.001$). For Germany, we identified 2,920 FT cases. The share of FT increased from 0.7% in 2006 to 2.0% in 2019 ($p < 0.001$). The number of RFAs in the USA steadily increased by 227% from a total of 93 in 2006 to 304 in 2019 while the number of cryotherapies in the USA steadily increased by 289% from a total of 127 in 2006 to 494 in 2019 ($p < 0.001$). The number of RFAs in Germany increased by 344% from a total of 59 in 2006 to 262 in 2019 ($p < 0.001$) while the number of cryotherapies steadily increased by 43% from a total of 54 in 2006 to 77 in 2019 ($p < 0.001$). In Germany, RFA is significantly more performed than cryotherapy while in the USA cryotherapy is more frequently applied. ***Conclusion:*** We observed a constant increase of FT in the USA and Germany for RCC in-patient treatment with a higher share in the USA.

Introduction

Renal cell carcinoma (RCC) represents around 3% of all cancers and remains one of the most lethal urological malignancies despite advances in surgical techniques and systemic treatment [1]. Nowadays, most renal tumors are incidentally detected due to the widespread use of cross-sectional imaging and therefore the majority are diagnosed at localized early stage [2, 3]. Classical curative therapy options are nephron-sparing surgery for smaller T1a tumors and if feasible for T1b

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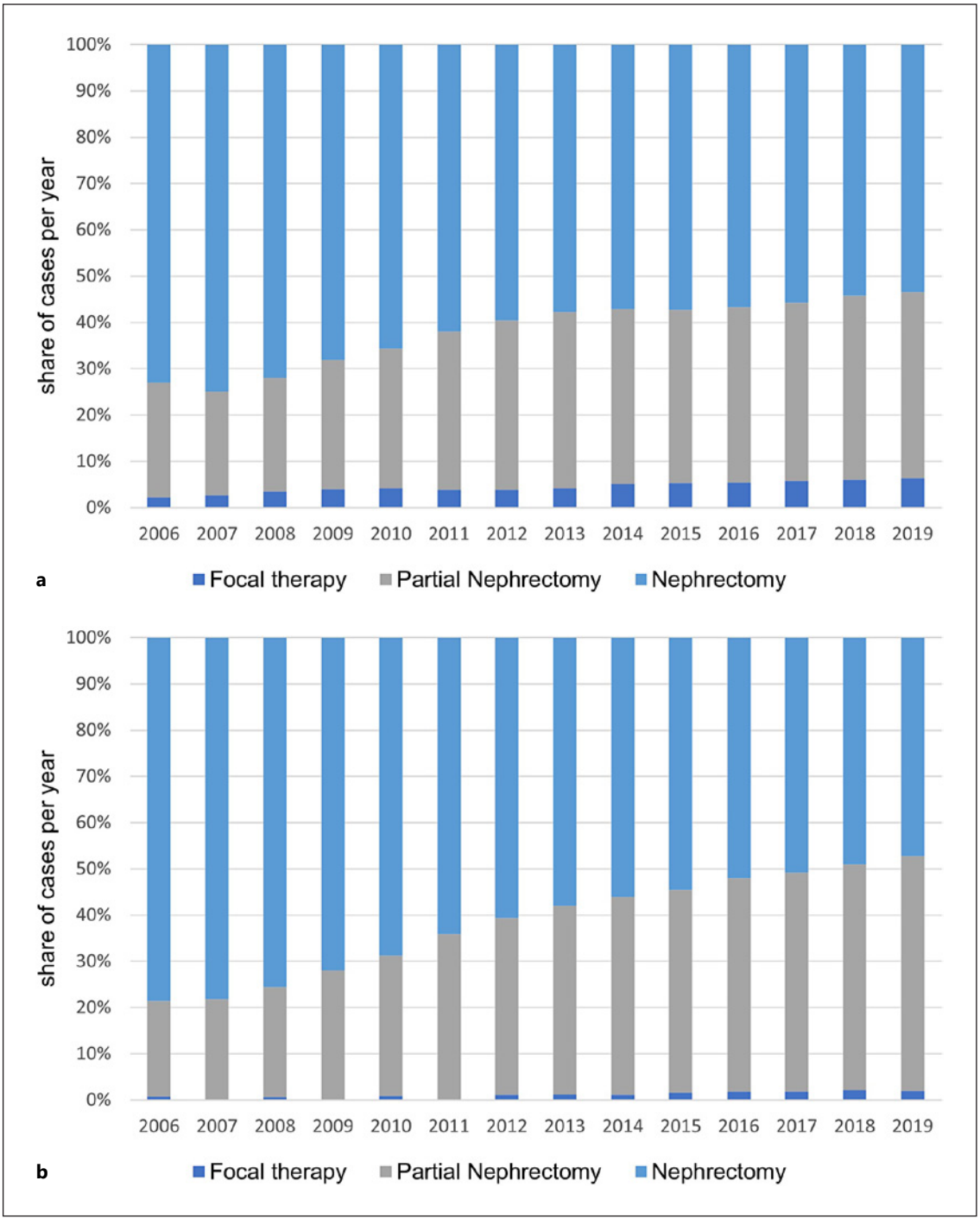

Fig. 1. Share of performed therapies for renal tumors in the USA (**a**) and Germany (**b**) (source: SEER database and Destatis data).

tumors while radical nephrectomy is recommended in larger renal tumors [4]. Alternative treatment options are active surveillance strategies or focal therapy (FT) [5, 6]. Different FT approaches are nowadays available with radiofrequency ablation (RFA) and cryotherapy being the most common procedures. Especially in older patients with relevant comorbidities, FT can be a good alternative treatment approach offering excellent

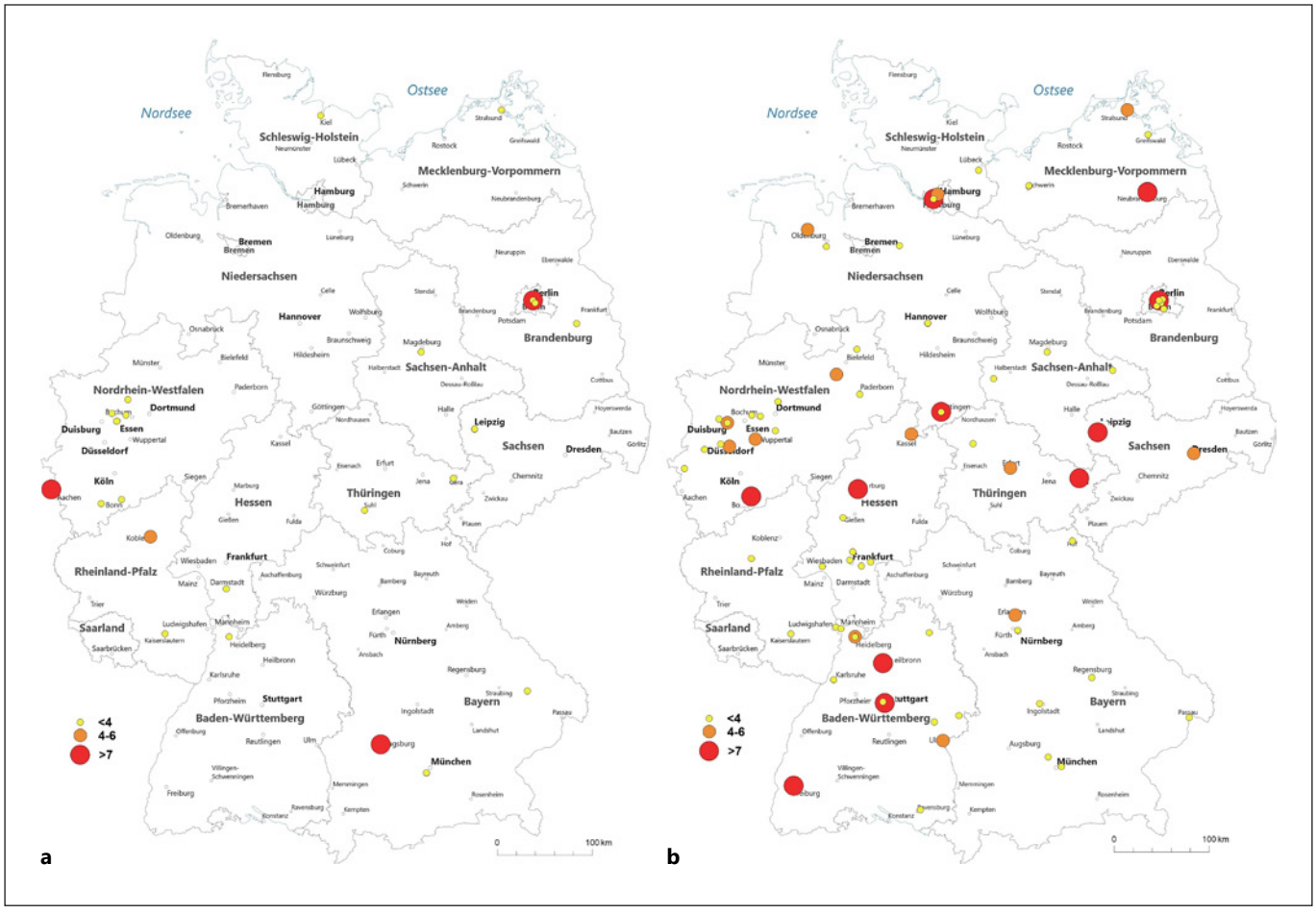

Fig. 2. Overview of performed RFA in 2006 (**a**) and 2020 (**b**) in Germany (source: German hospitals' quality reports).

Table 1. Overview of the queried databases

Country	USA	Germany	
Data source	SEER database (cancer registry)	Nationwide hospital billing database of the German Federal Statistical Office (Destatis database)	German hospitals' quality reports (reimbursement.INFO tool)
Data details	Diagnosis code	Age and gender	Age and gender
	Pathologic T stage	Diagnosis code	Type of surgery
	Treatment information from cancer registry data	Type of surgery and approach	Hospital characteristics (teaching status, annual surgery caseload)
		Hospital characteristics (teaching status, size, annual surgery caseload, approaches for surgery)	Geographical localization of respective hospitals
Patients, *n*	7,318	2,920	2,224
Proportion of the country, %	28	100	100
Included years	2006–2019	2006–2019	2006–2020 (missing: 2007, 2009, 2011)

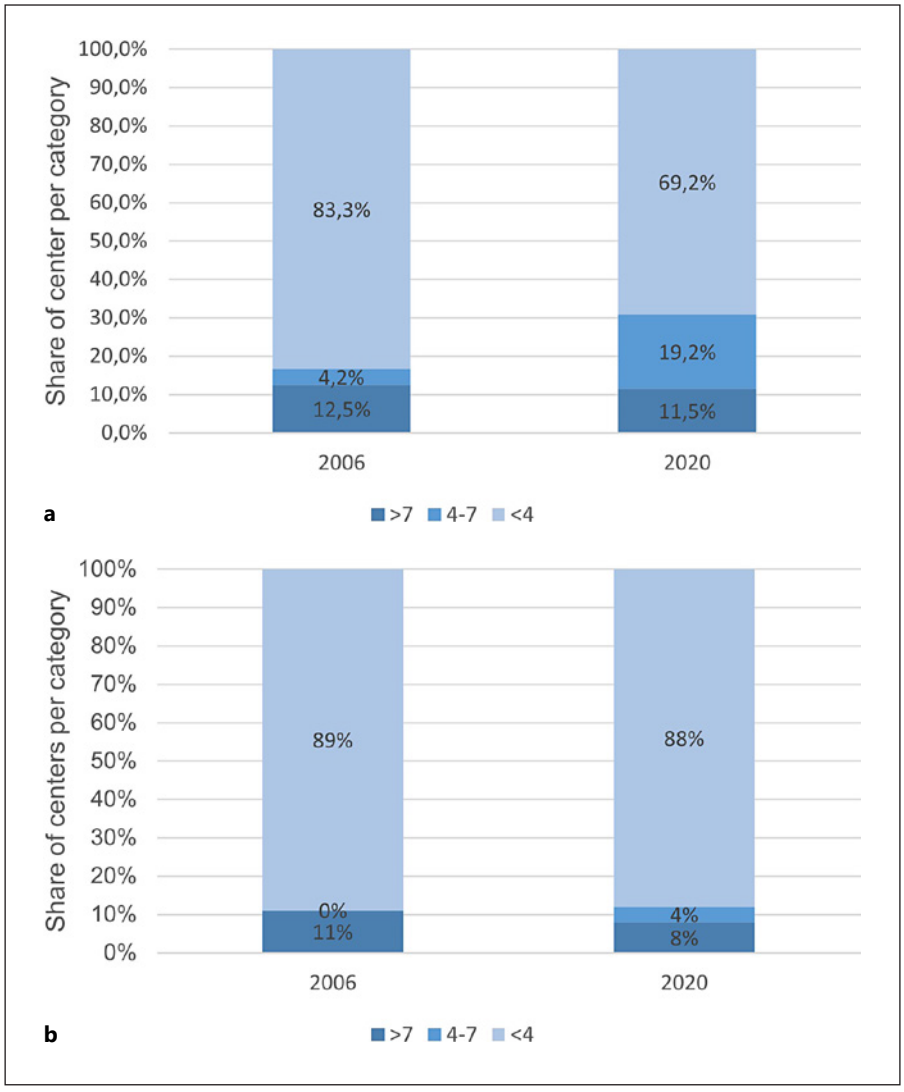

Fig. 3. RFA (**a**) and cryotherapy (**b**) annual procedures in 2006 and 2020 by share of centers per category (source: German hospitals' quality reports).

oncological results [7]. The European Association of Urology (EAU) guidelines as well as the American Association of Urology (AUA) guidelines recommend focal approaches in patients with RCC who are unfit for surgery [4, 8]. RFA has been available for treatment of soft-tissue tumors since the early 1990s with special focus on hepatic malignancies [9]. First applications of RFA for renal tumors were described by Gervais et al. [10] in 2000 showing promising results in small exophytic RCC tumors. By using high-frequency current flow, thermonecrosis leads to tissue destruction during the RFA procedure [11]. Cryotherapy is a further method of tumor ablation that was introduced in the 1990s. Uchida et al. first described ultrasound-guided percutaneous cryoablation in 1995 [12]. Shingleton et al. [13] reported minimal morbidity and good technical feasibility for percutaneous renal tumor cryoablation with MRI guidance. In addition, laparoscopic cryotherapy is a further option for RCC treatment.

Population-based studies investigating FT trends for RCC treatment are rare. Therefore, our goal was to describe trends of RCC management by FT in the USA and Germany from 2006 to 2019. Moreover, we aimed to analyze the respective German health care landscape in more detail.

Patients and Methods

Table 1 provides an overview of the queried databases. For the USA, we queried the Surveillance, Epidemiology, and End Results (SEER) database. We analyzed data from German hospitals' quality reports and from the German billing database

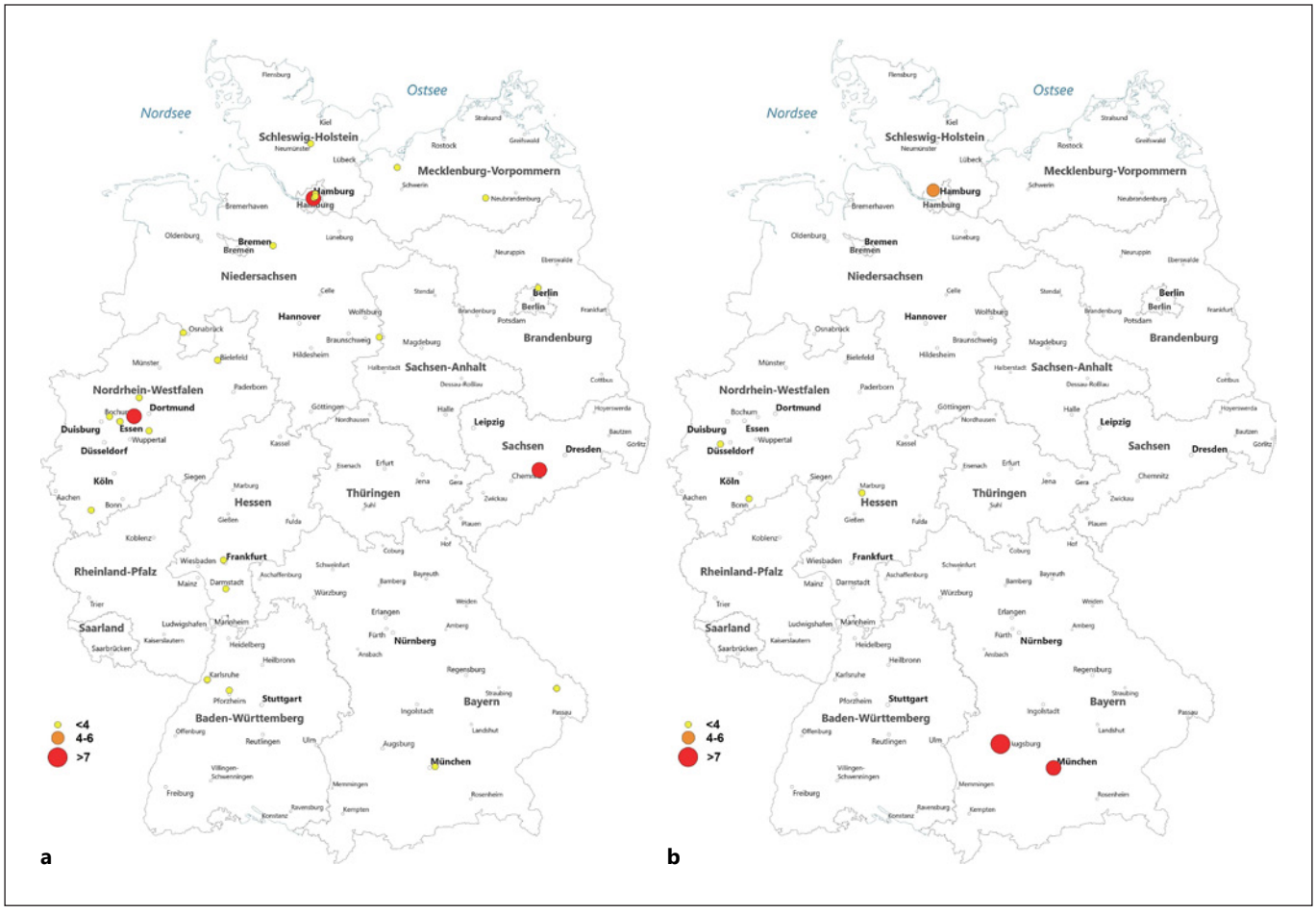

Fig. 4. Overview of performed cryotherapy in 2006 (**a**) and 2020 (**b**) in Germany (source: German hospitals' quality reports).

(Destatis). The German hospitals' quality reports were used for identification of national providers while the Destatis database was used for analysis of all FT procedures. The cohort identification as well as the way of data extraction has been previously described [14, 15].

Surveillance, Epidemiology, and End Results Database

The SEER database collects data on patients diagnosed with cancer, using 17 population-based cancer registries, which represent approximately 28% of the population of the USA [15]. SEER data are an open access resource for cancer-based epidemiology and survival analyses. SEER*Stat software from the National Cancer Institute (SEER*Stat software, http://www.seer.cancer.gov/seerstat, version 8.4.0.1) was used to identify eligible patients. The dataset was released in April 2022. We obtained permission to access these research data files with the reference number 14362-Nov2021. Patients were identified based on the International Classification of Diseases for Oncology, Third Edition (ICD code C64.9 – primary tumor location kidney) in combination with surgical codes (SEER codes 13 and 23 – cryotherapy, SEER code 15 – RFA, SEER code 30 – partial nephrectomy, and SEER codes 40, 50, 70, 80 – nephrectomy) from 2006 to 2019. We excluded patients aged <18 years at the time of diagnosis.

German Billing Database (Destatis)

Reimbursement data of in-patient treatment are collected in Germany since 2004 by the German Federal Statistical Office (Destatis). All German hospitals are obliged by law to transmit these data to Destatis, which is why this database represents a total population sample. We included patients with the diagnosis of renal cancer (ICD code "C64.0"), a neoplasm of uncertain behavior of urinary organs (ICD code "D41.0"), a benign neoplasm of the urinary organs (ICD code "D30.0") in combination with FT (OPS code "5-552.50" – RFA from 2016 to 2019, OPS code "5-552.8" – RFA from 2006 to 2015, OPS code "5-552.52" – cryotherapy from 2016 to 2019). Since there was no exact OPS code representing cryotherapy before 2016, we analyzed the OPS code "5-552.5" (percutan-transrenal destruction) from 2006 to 2015. We further analyzed OPS codes "5-553 – partial nephrectomy" and "5-554 – nephrectomy" as well as "5-987" to identify robot-assisted procedures.

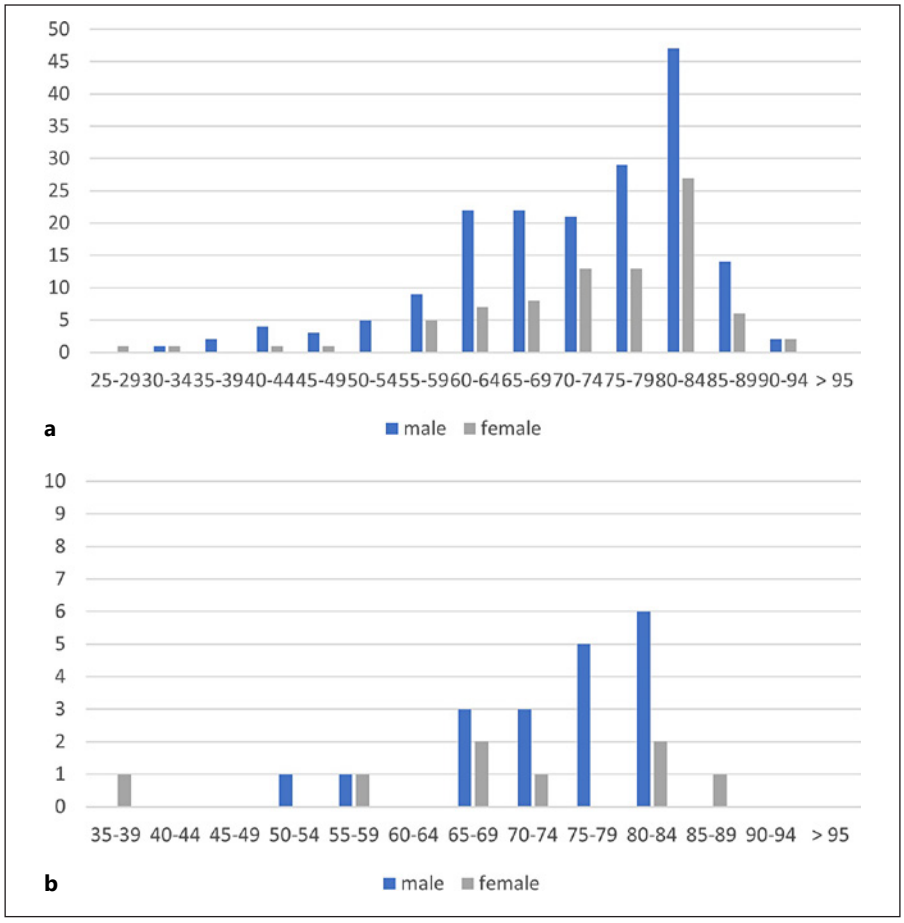

Fig. 5. RFA (**a**) and cryotherapy (**b**) in 2020 stratified by age distribution (source: German hospitals' quality reports).

German Hospitals' Quality Reports

FT was analyzed on an institutional level with the reimbursement.INFO tool (Reimbursement Institute, Hürth, Germany) based on billing data from hospitals' quality reports. We used OPS code "5-552.50" – RFA from 2016 to 2020, OPS code "5-552.8" – RFA from 2006 to 2015, OPS code "5-552.52" – cryotherapy from 2016 to 2020, OPS code "5-552.5" – cryotherapy from 2006 to 2015. Maps were created by using the software "EasyMap 11.1 Standard Edition" (Lutum + Tappert DV-Beratung GmbH, Bonn, Germany).

Statistical Analysis

Data were presented by absolute and relative frequencies. For comparison of groups, we applied χ^2 test. To detect trends over time, linear regression models were implemented. We defined $p < 0.05$ to indicate statistical significance. We used SPSS 28.0.1.1 (IBM Corp., Armonk, NY, USA) for statistical analysis.

Ethics Statement

The data presented in this study were obtained in accordance with the World Health Association Declaration of Helsinki in its latest version. Since the data extracted from the databases were anonymized and de-identified prior to release, our study did not require patient informed consent and an additional ethics statement was not required.

Results

From the USA, we included 7,318 FT cases (2832 RFA and 4486 cryotherapy) and from Germany we analyzed 2,920 FT cases (2160 RFA and 760 cryotherapy). Figure 1 displays the share of performed therapies for renal tumors in Germany (Fig. 1b) and USA (Fig. 1a). The share of FT increased from 2.4% in 2006 to 6.4% in 2019 in the USA ($p < 0.001$). In Germany, the share of FT increased from 0.7% in 2006 to 2.0% in 2019 ($p < 0.001$). In the USA, the share of partial nephrectomy increased to 40.1% in 2019 and in Germany to 51.0% in 2019 ($p < 0.001$).

The number of RFAs in the USA steadily increased by 227% from a total of 93 in 2006 to 304 in 2019 ($p < 0.001$). The number of RFAs in Germany steadily increased by 344% from a total of 59 in 2006 to 262 in 2019 ($p < 0.001$). Figure 2 gives an overview of German hospitals performing RFA in 2006 (Fig. 2a) and 2020 (Fig. 2b), respectively. 24 urological departments performed RFA in 2006 and 78 urological departments performed RFA in 2020. In 2006, 3 of 24 hospitals (12.5%) performed >7 RFAs/per year

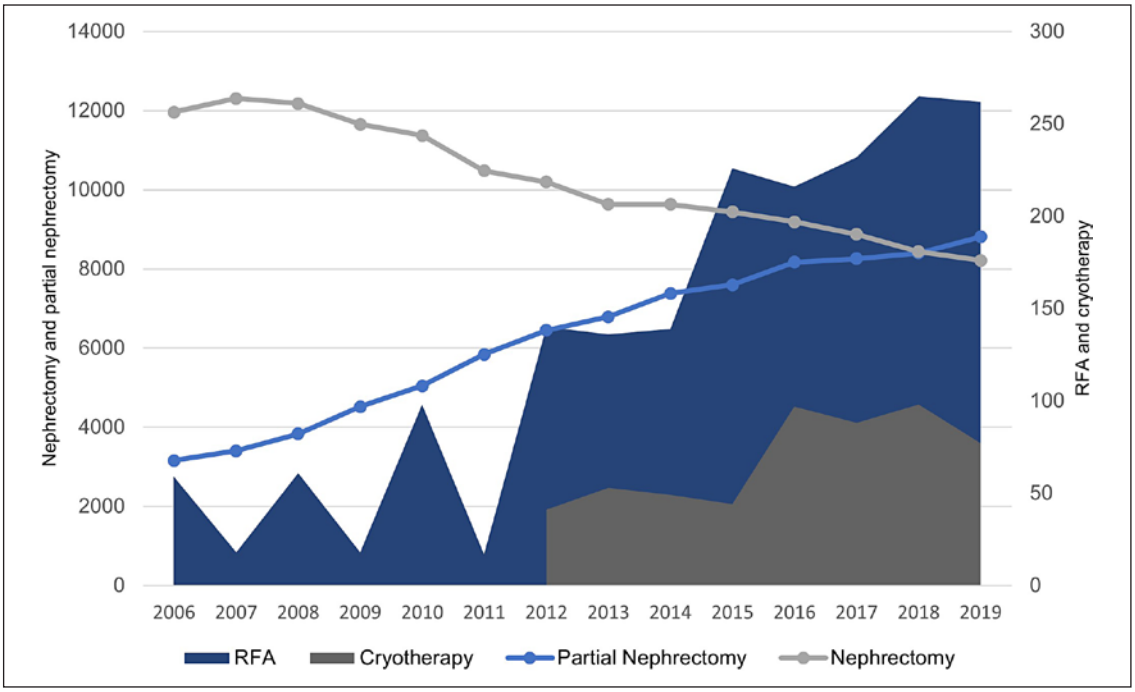

Fig. 6. Overview of trends for RCC treatment from 2006 to 2019 (source: Destatis data).

which slightly decreased to 9 out of 78 hospitals (11.5%) in 2020. In 2020, 15 out of 78 hospitals (19.2%) performed 4–7 RFAs/year and 54 out 78 hospitals (69.2%) performed <4 RFAs/year ($p = 0.2$) (Fig. 3a).

The number of cryotherapies in the USA steadily increased by 289% from a total of 127 in 2006 to 494 in 2019 ($p < 0.001$). The number of cryotherapies in Germany steadily increased by 43% from a total of 54 in 2006 to 77 in 2019 ($p < 0.001$). Figure 4 displays an overview of German hospitals performing cryotherapy in 2006 (Fig. 4a) and 2020 (Fig. 4b), respectively. 27 urological departments performed cryotherapy in 2006 and 25 urological departments performed cryotherapy in 2020. In 2006, 3 out of 27 hospitals (11.1%) performed >7 cryotherapies/year which decreased to 2 out of 25 hospitals (8%) in 2020. In 2020, 1 out of 25 hospitals performed 4–7 cryotherapies (4%) and 22 hospitals (88%) performed <4 cryotherapies/year ($p = 0.92$) (Fig. 3b).

In 2006, 45.8% (11/24) of RFAs were performed at a university hospital which decreased to 23.1% (18/78) in 2020. However, from the top 10 most performing hospitals (RFA) 50% were university hospitals in 2020. In 2006, 7% (2/27) of cryotherapies were performed at a university hospital which increased to 52% (13/25) in 2020. In 2020, 67.8% of treated patients with RFA were male (female 32.2%) and 76.4% of all treated patients (female and male) were older than 65 years of age (Fig. 5a). In 2020, 70.4 of patients treated with cryotherapy were male (female 29.6%) and 85.2% were older than 65 years of age (Fig. 5b). Figure 6 gives a detailed overview of trends for RCC treatment in Germany from 2006 to 2019. We observed an increase in caseload of partial nephrectomy.

Discussion

We investigated treatment trends of FT for renal tumors in the USA and in Germany from 2006 to 2020. Our results showed that the share of FT steadily increased in both countries. While in the USA cryotherapy is the favored FT approach, RFA is more commonly performed in Germany. In line with our results, a recent study from the USA investigating Medicare data showed an increase of percutaneous ablation procedures by 80% between 2010 and 2018 [16].

Guideline Recommendations, FT in the Elderly, and Safety

FT as well as active surveillance are established alternatives to surgical approaches in patients with pT1a RCC [4, 8]. However, several studies that compared oncological outcomes as local recurrence or overall survival between FT and partial nephrectomy for patients with RCC showed

no compelling evidence in favor of RFA or cryotherapy [17]. Therefore, the EAU guidelines as well as the AUA guidelines recommend partial nephrectomy for RCC as a standard treatment [4, 8]. In accordance with these recommendations, we observed in the present study a steady increase of partial nephrectomy for management of RCC in both countries. However, the guidelines suggest FT for older, frail patients with comorbidities. Our results showed that 76.4% of all treated patients with RFA were older than 65 years while for cryotherapy 85.2% were older than 65 years. Aron et al. [18] presented advantages of FT in the elderly such as a short hospitalization time, a reduced morbidity, as well as a good tolerability in patients with severe comorbidities. FT might also be a good option for highly selected younger patients with multiple tumors and very high recurrence risk like in the case of von Hippel-Lindau syndrome [19]. Uhlig et al. [20] performed a systematic review and meta-analysis showing that patients receiving RFA, cryotherapy, or microwave ablation were older and had more comorbidities. Besides a superior complication profile in certain patients, the authors also emphasized preservation of renal function after FT for RCC. However, the meta-analysis also showed that the risk for local recurrence was nearly doubling after FT when compared with partial nephrectomy [20]. A recently published national register study from Sweden showed similar results. Patients treated with ablative techniques (RFA, cryotherapy) had a significantly higher rate of local recurrence (30 of 169, 17.8%) than patients treated with radical or partial nephrectomy [21]. Therefore, current guidelines recommend FT only for older patients who are unfit for surgery. Further, a multi-institutional study showed low complication profile and good safety of FT in RCC treatment compared to surgical approaches. Local pain at the insertion site was mostly reported [22].

Radiofrequency Ablation

Radiofrequency energy causes high-frequency current flow from an active electrode tip into the surrounding tissue. This leads to ion agitation, molecular friction, cellular warming with coagulative tumor necrosis by protein denaturation, and immediate cell death [11, 12]. Our results showed that in Germany RFA was the dominant FT for RCC increasing by 344% from 2006 to 2020. While in 2006 only 24 hospitals offered RFAs for RCC, the number increased to 78 hospitals in 2020. Johnson et al. [23] reviewed long-term oncologic outcomes after RFA treatment showing good oncological outcomes with 10-year survival data. In 106 patients, no recurrence developed after 5 years. Our analysis showed that every second hospital offering RFA in 2020 in Germany was an academic hospital. Furthermore, those university hospitals performed the highest annual caseload. Sato et al. [24] investigated the association between hospital volume and in-hospital mortality following RFA for hepatocellular carcinoma. The authors were able to show that in-hospital mortality was significantly higher in low-volume hospitals. Therefore, the observed trend toward centralization of RFA in Germany to high-volume centers might provide better oncological outcomes and increase patient safety. In the USA, we observed a slight increase of RFA cases from a total of 93 in 2006 to 304 in 2019 ($p < 0.001$). Similar results were recently published by Patel et al. analyzing a Medicare sample with an increase of percutaneous RFA from 1105 in 2010 to 1590 procedures in 2018 (43.9%) [16].

Cryotherapy

Cryotherapy is an ablative technique which was first described for treatment of RCC in 1996 via the open approach [25]. In 1998, Gill et al. [26] performed the first laparoscopic cryoablation of an RCC. Percutaneous ultrasound-guided cryotherapy was introduced in 1995 by Uchida et al. [13]. Cryotherapy causes tissue necrosis in the targeted tissue by the freeze cycle which leads to intra- and extracellular ice formation followed by a thaw cycle leading to osmotic cellular phospholipid membrane rupture [27]. In general, the freeze-thaw cycle is repeated twice. Nowadays, percutaneous cryoablation became the dominant focal technique for RCC in the USA [16]. Our SEER analysis showed an increase of cryotherapy from a total of 127 cases in 2006 to 494 in 2019 ($p < 0.001$). For Germany, we observed a slight increase in cryotherapies by 43% from a total of 54 in 2006 to 77 in 2019 ($p < 0.001$). Rosenberg et al. [28] identified two factors that are mainly responsible for cryotherapy becoming the preferred FT for RCC in the USA. First, the procedure demonstrated high safety with a low risk of collecting system injury. Second, procedure time of percutaneous cryotherapy is significantly shorter compared to other FTs [16]. The average reimbursement for percutaneous cryoablation in 2018 was $481 [16]. In 2020, 2 out of 25 hospitals performed >7 cryotherapies/year in Germany. Due to the small number of cases, it is difficult to describe a centralization of the procedure.

By analyzing our created maps about the distribution of FT for RCC, we observed that RFA was offered in all major regions in Germany whereas cryotherapy was only found in selected areas (predominantly in the south). We assume that RFA was the preferred FT approach in Germany due to lower risk of local recurrence and less deterioration of renal function [20]. In contrary, cryotherapy which was the dominant FT in the USA could be favored due to shorter operation time and estimated blood loss as well as better

reimbursement compared to RFA ($358 for percutaneous RFA and $481 for percutaneous cryoablation in 2018) [16]. Furthermore, the different health care systems in the USA and Germany are most likely also related to the marked difference in preference of FT technique as well as the share of FT [14]. One possible explanation for the higher share of FT in the USA could be that percutaneous RFA or cryotherapy can be offered in an outpatient setting with lower costs and less morbidity for the patient.

Limitations

Limitations of this study include its retrospective and observational nature. Additionally, the German databases lack clinical details on patient and tumor characteristics. Further, the comparison is limited since for the USA we analyzed a cancer registry and for Germany hospital billing data. However, this is the first study comparing FT trends for RCC between the USA and Germany over an extensive study period. Unfortunately, there was no OPS code for cryotherapy prior to 2016 available in Germany, so we adjusted and used a less specific code for previous years leading to a possible selection bias. Furthermore, there is no code to analyze the use of active surveillance, which offers an alternative in patients with small RCC. Finally, we only included in-patient data; therefore, we were not able to cover patients receiving focal RCC treatment in an ambulatory setting. Keeping these limitations in mind, we were able to show the first international contemporary trends of FT for RCC management over a 15-year time span.

Conclusion

This longitudinal population-based study showed that the share of FT for RCC treatment increased in Germany and the USA. Interestingly, in Germany RFA is more commonly performed while in the USA cryotherapy is the dominant FT for RCC. As recommended by the AUA and EAU guidelines, the majority of patients undergoing RFA or cryotherapy are older than 65 years of age. In Germany, both FT approaches are mostly performed by academic hospitals.

Acknowledgments

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Statement of Ethics

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. Since the data extracted from the databases were anonymized and de-identified prior to release, our study did not require patient informed consent and an additional ethics statement was not required. Ethical approval and consent is also not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

Luka Flegar certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership, expert testimony, royalties, or patents filed, received, or pending), are the following: none. N. Eisenmenger is founder and director of RI Innovation GmbH. J. Huber is managing director of the Urologische Stiftung Gesundheit gGmbH and indicates support of scientific projects outside the submitted work by Intuitive Surgical, Takeda, Janssen, and Coloplast. All the other authors have no conflicts of interest to declare.

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Author Contributions

All authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results. Study concept and design: Dr. Luka Flegar. Acquisition of data: Dr. Luka Flegar, Smita Thoduka, PD Christer Groeben, and Nicole Eisenmenger. Analysis and interpretation of data: Dr. Luka Flegar, Smita Thoduka, Dr. Jens Figiel, and Dr. Aristeidis Zacharis. Drafting of the manuscript: Dr. Luka Flegar, Dr. Aristeidis Zacharis, Prof. Dr. Andreas H. Mahnken, Dr. Hendrik Heers, Dr. Cem Aksoy, and Prof. Dr. Johannes Huber. Critical revision of the manuscript for important intellectual content: all authors. Supervision: Prof. Dr. Johannes Huber.

Data Availability Statement

All datasets used in this work are stored centrally at the specific institutes (German Federal Statistical Office – Destatis; German National Centre for Cancer Registry data at the Robert-Koch Institute). All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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