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INTEGRATED STUDY MASTER'S FINAL THESIS

Laparoskopinės ir robotu asistuojamos inkstų reyekcijos palyginimas su inkstų krioabliacija. Literatūros apžvalga

Comparison of Laparoscopic and Robot Assisted Partial Nephrectomy with Kidney Cryoablation. Literature Review

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1. SUMMARY

This thesis incorporates 11 articles published since 2020 focusing on laparoscopic partial nephrectomy, robot assisted partial nephrectomy and cryoablation for T1a and T1b renal cell carcinomas. This time frame has been chosen to ensure that incorporated studies were not extensively assessed and incorporated into systematic reviews and meta-analyses and therefore represent the most recent developments regarding this topic. A comprehensive literature retrieval of the PubMed database was conducted by using a Boolean string to identify relevant literature. Initially 111 articles were identified and further processed. For primary sources of this thesis, systematic reviews and meta-analyses, case series, narrative reviews and trial protocols were excluded to ensure that no double presentation of studies occur, results are available, and the results are representative of a wider population, rather than only depicting a series of cases. Using a variation of the PICO framework the initial 111 articles were further screened excluding articles which did not match the outlined. Methodological excerption of relevant information and thorough incorporation into excel sheets was performed. Relevant findings have been displayed in tables providing a well-structured overview over every single study as well as granting the possibility to directly compare the studies in a narrative approach. Most findings have also been described in written text while some findings a restricted to the tables for better readability. Thorough analyzing of the exerted data lead to the discussion of the weaknesses and strengths of the methods as well as of the written thesis itself. Strengths are the well-structured and reproducible literature retrieval, thorough presentation of materials and methods as well as implementation of comparing findings with published literature. Important is the identification of variations of included patients for each treatment modality highlighting the concept of individualized treatments based on factors such as age or renal function. Sadly, this thesis also identified the gap the representation of the female sex in medical studies. Interestingly, paradox findings have been identified within the studies as compared to already published systematic reviews and meta-analyses. Weaknesses were the amount of available literature and the limitations in direct comparison due to variations in values and lack of data presented by the studies. This thesis concludes that the ongoing development of new treatment modalities warrants ongoing research so that physicians have the possibility to offer patients individualized treatment options suiting every patient. Underrepresentation of patient groups such as the elderly, females, and patients with comorbidities should be considered an appeal for future research, including more previously underrepresented patients.

Šiame darbe apžvelgiama 11 straipsnių, paskelbtų nuo 2020 m. Juose daugiausia dėmesio skiriama laparoskopinei inksto rezekcija, robotų pagalba atliekamai inksto rezekcija ir krioabliacijai -

technikoms, taikomoms T1a ir T1b stadijų inkstų ląstelių karcinomoms gydyti. Pastarųjų metų laikotarpis pasirinktas siekiant užtikrinti, jog atrinktieji tyrimai dar nebūtų išsamiai įvertinti ir įtraukti į sistemines apžvalgas bei metaanalizes - tad jie atspindi naujausius minėtosios srities pokyčius. Bandant atrasti tyrimui tinkamą literatūrą, buvo atlikta išsami paieška PubMed duomenų bazėje, naudojant Būlio išraišką. Iš pradžių buvo rasti ir peržvelgti 111 straipsnių. Tuomet atmestos sisteminės apžvalgos ir metaanalizės, atvejų serijos, aprašomosios apžvalgos bei tyrimų protokolai norint užtikrinti, jog tyrimai nebūtų pateikiami dukart, o rezultatai būtų prieinami ir atspindėtų kuo įmanoma platesnę populiaciją, ne tik atvejų seriją. Naudojant PICO modelio variantą, pradiniai 111 straipsnių atrinkti toliau, kita dalis atmesta dėl kriterijų neatitikimo. Informacija buvo atrinkta metodologiškai ir suvesta į Excel lenteles. Atitinkami rezultatai pateikti lentelėse, padėjusiose struktūrizuotai apžvelgti kiekvieno tyrimo esmę bei tiesiogiai palyginti tiriamuosius. Dauguma bendrųjų rezultatų aprašyti tekste. Išsamiai išanalizavus pateiktus duomenis, aptariami metodų bei pačios disertacijos privalumai ir trūkumai. Tarp stipriųjų pusių - gerai struktūruotas ir pakartojamas literatūros paieškos procesas, išsamus medžiagų ir metodų pristatymas bei rezultatų palyginimas su jau esama literatūra. Taip pat pravartu, jog buvo galima nustatyti įtrauktųjų pacientų skirtumus, aktualius gydymo būdo pasirinkimui - tai pabrėžia individualizuotos medicinos koncepciją, pagrįstą tokiais veiksniais kaip amžius ar inkstų funkcija. Visgi, šiame darbe taip pat buvo pastebėta moterų atstovavimo medicininiuose tyrimuose spraga. Įdomu tai, kad tyrimuose nustatyti paradoksalūs rezultatai, palyginti su jau paskelbtomis sisteminėmis apžvalgomis ir metaanalizėmis. Tad trūkumai buvo susiję su esamos literatūros kiekiu bei tiesioginio palyginimo apribojimais dėl verčių skirtumų ir duomenų stygiaus tyrimuose. Šioje disertacijoje daroma išvada, jog nuolatinis naujų gydymo būdų kūrimas reikalauja tolimesnių tyrimų tam, kad gydytojai galėtų pasiūlyti pacientams jiems pritaikytas - individualizuotas - gydymo galimybes. Nepakankamas įvairių pacientų grupių, tokių kaip pagyvenę žmonės, moterys ir sergantieji gretutinėmis ligomis, atstovavimas turėtų būti laikomas aiškiu perspėjimu ateities tyrimams įtraukti daugiau anksčiau nepakankamai reprezentuotų pacientų.

2. KEYWORDS

Comparison, Laparoscopic Partial Nephrectomy, LPN, Robot Assisted Partial Nephrectomy, RAPN, Kidney Cryoablation, CA, Literature Review

3. ABBREVIATIONS

ASR = Age-standardized rate
BMI = Body mass index
CA = Cryoablation

CD = Clavien-Dindo

CI = Confidence interval

CSS = Cancer-specific survival

DM = Distant metastasis

EAU = European association of urology

EBL = Estimated blood loss

eGFR = Estimated glomerular filtration rate

FT = Focal Therapy

IQR = Interquartile range

LOS = Length of stay

LPN = Laparoscopic partial nephrectomy

LR = Local recurrence

LRFS = Local-recurrence-free survival

MFS = Metastasis-free survival

MIPN = Minimal invasive partial nephrectomy

NA = Not available/applicable

OS = Overall survival

OT = Operative time

PCA = Percutaneous cryoablation

PICO = Patient/population, intervention, comparison, outcome

PN = Partial nephrectomy

RAPN = Robot-assisted partial nephrectomy

RCC = Renal cell carcinoma

sCr = Serum creatinine

SD = Standard deviation

SRM = Small renal mass

4. INTRODUCTION

Europe is the second highest region globally when it comes to age-standardized rate for kidney cancer incidence and the highest when it comes to mortality. In 2022, Europe reported an ASR of 9.7 for the incidence and an ASR of 2.7 for the mortality (1). This information highlights the importance of understanding the epidemiology, optimizing diagnostic approaches, and improving treatment strategies of kidney cancer. More than 90% of kidney cancers can be contributed to renal cell carcinomas (RCC) (2), making this etiology the most common, hence in the following solely renal cell carcinomas are considered whenever kidney cancer is mentioned without further discrimination of subtypes, while it should be mentioned, that prognosis is primarily dependent on the pathological stage, the histology, and grade (2).

4.1 INCREASED INCIDENCE OF KIDNEY CANCER

One contributor frequently mentioned in literature contributing to the rising incidence of kidney cancer is the increased use of cross-sectional abdominal imaging, which leads to a higher detection rate of small renal masses (3). Approximately 70% of these detected masses are stage I renal cell carcinomas (RCC) (4), furthermore 50% of renal masses are found incidentally in asymptomatic patients who undergo imaging due to various unrelated reasons (2,5). However, up to 20% of small renal masses (SRM), meaning tumors ≤ 4cm in size, are misclassified as malignant while they are, in fact, benign (4), raising concerns regarding the clinical relevance of such findings and highlighting the potential role of active surveillance as an alternative to immediate treatment for some patients. In addition to increased detection, the rising incidence of RCC is linked to the prevalence of modifiable risk factors which include smoking, obesity, hypertension, end-stage renal disease, and occupational exposure to trichloroethylene (5,6). Actions to reduce these modifiable risk factors, like smoking cessation and proper management of hypertension and obesity, remain the primary prevention measures for RCC (5). Demographic changes are also considerable. Since RCC notes its highest incidence among the older population (7), this demographic shift underlines the need for both safe and effective treatment modalities that also consider the additional challenges which come in the treatment of elderly, such as increased surgical risks, comorbidities, and preexisting kidney disease.

4.2 CURRENT TREATMENT GUIDELINES AND CHALLENGES

The 2024 European Association of Urology (EAU) guidelines on RCC strongly recommend partial nephrectomy (PN) for patients with T1 RCC, meaning ≤ 7 cm of size. They also emphasize that the choice of surgical approach, such as laparoscopic partial nephrectomy (LPN) or robot-assisted partial nephrectomy (RAPN), should be based on the surgeon´s experience. As an alternative approach to surgery, thermal ablation has been considered as a method only for frail and/or comorbid patients with SRM, this decision is based on the availability of only low-quality evidence (7).

4.3 RESEARCH GAP AND THESIS OBJECTIVE

Despite the availability of existing treatment recommendations for PN in patients with RCC, uncertainties remain concerning the treatment of patients with specific factors, such as comorbidities, renal function, and the patients will, making the need for individualized treatment approaches undeniable.

This thesis evaluates the current state of research on the outcomes of LPN, RAPN, and cryoablation (CA) for T1 RCC. By considering available data from accessible articles on variables such as oncological outcomes, renal function preservation, and perioperative complications, the aim of this thesis is to establishing a profound overview on the advantages and limitations which could ultimately help in offering are more tailored treatment strategy for patients who are affected by this disease.

5. CURRENT STATE OF RESEARCH

Treatment modalities for renal cell carcinoma have been subject for research in the past and there are various articles addressing differences between various treatment modalities, highlighting possible advantages as well as disadvantages. In the following, a comprehensive overview about the most recent systematic reviews and meta-analyses regarding differences between treatment modalities for RCCs is presented. This is done to establish knowledge regarding the current state of research as well as to identify gaps within the currently available systematic reviews and meta-analyses.

5.1 DONG ET AL. (2022)

Dong et al. published a systematic review and meta-analysis in 2022 which compares the outcomes of minimal invasive partial nephrectomies (MIPN) and focal therapies (FT) for small renal masses. Interventions included in the MIPN group were robot assisted partial nephrectomy and laparoscopic partial nephrectomy, while the FT group included radiofrequency ablation, cryoablation (CA), microwave ablation, and irreversible electroporation. The authors assessed perioperative outcomes such as operative time (OT), estimated blood loss (EBL), length of stay (LOS), and minor and major complications according to the Clavien classification. In which minor classifications were attributable to Clavien 1-2 and major to Clavien 3-5. (8)
The original Clavien classification only described four grades of severity. Grade 1 were considered complications which do not need any therapy expect for medications against pain, fever, nausea, diarrhea or infections of the lower urinary tract. Clavien 2 need prolonged hospital stay they could be

potentially putting the patient at a life-threatening risk. Furthermore, grade 2 is subdivided into 2a and 2b requiring either medications or interventions respectively. The grade 3 of the Clavien classification require further resection of an organ or may leave the patient with disability. The final 4th grade is considered a complication through which the patient has died. (9)
It appears as that Dong et al. have counted 2a and 2b as two different complication classifications since they stated a total of 5 grades in their publication.

The renal functional outcome was assessed using the estimated glomerular filtration rate (eGFR). Assessed oncological outcomes were local recurrence (LR) and distant metastasis (DM) rate.
A total of 26 studies were included in the article, encompassing a total of 4.420 participants, which can be divided into 2.031 for MIPN and 2.389 for FT. The latter displayed superiority over MIPN regardless of the performed technique in terms of a shorter OT, lower EBL, shorter LOS, fewer minor (Clavien 1-2) and overall complications and more favorable renal function preservation. No difference was found regarding major complications (Clavien 3-5). The authors reported the oncological outcomes in terms of LR and rate of DM, which were similar between MIPN and FT. The follow-up periods were presented with median or mean. For MIPN they reported them to be 2.2 to 42.7 months and for FT they were 14 to 78 months. (8)

To summarize the previously mentioned findings, FT demonstrates superiority in protecting kidney function, reducing bleeding, shortening the OT and shorten the LOS in total, but FT is neither non-superior nor non-inferior in terms of LR, DM, and major complications. While this systematic review and meta-analysis provides a comprehensive overview over advantages of FT in general over MIPN, it lacks a more detailed comparison of specific subtypes, despite displaying separate outcomes for RAPN and LPN in cases of high heterogeneity.

5.2 NOWAK ET AL. (2024)

A systematic review and meta-analysis published in 2024 by Nowak et al. narrows the previously mentioned gap by addressing percutaneous cryoablation (PCA) and comparing it to partial nephrectomy in patients with a cT1 renal tumor. While patients with both cT1a and cT1b were included in the article, most patients had cT1a tumors. The authors assessed complications, renal function as eGFR preservation and/or change after surgery and oncological outcomes as local recurrence-free survival (LRFS), metastasis-free survival (MFS), cancer-specific survival (CSS) and overall survival (OS). They included 14 studies with a total of 6.487 participants, divided into 1.554 (23.9%) in the PCA group and 4.924 (76.1%) in the PN group. Regarding the overall complication rate, they found, that in patients who underwent PCA, fewer overall complications occurred. This finding is also consistent when assessing the major complication rate (Clavien-Dindo (CD) ≥ 3), here PCA also shows significantly lower rates compared to PN.

The Clavien-Dindo classification from 2004 is a modified version of the previously mentioned Clavien classification of complications from 1992. The CD classification provides 5 grades with two subgroups for grade 3 and 4, resulting in a total of 7 grades compared to the total of 5 grades in the Clavien classification. Grade 1 encompasses any variation of the normal postoperative course which do not require any treatment except for medications against nausea or pain, electrolytes, diuretics, and therapy such as physiotherapy or incisions into wound infections performed outside the operation room. Grade 2 include further medical treatment. More complex interventions without or with general anesthesia are considered grade 3a and 3b respectively. When a patient requires treatment in the intensive care unit, they are considered 4a or 4b depending on whether a single organ is dysfunctioning or multiple organs have failed. The last grade is as for the Clavien classification the death of the patient. (9)

The authors reported no significant differences between PCA and PN regarding the differences in mean % eGFR preservation rates or mean change in eGFR after surgery.
When assessing the oncological outcomes, Nowak et al. reported significant differences regarding the LRFS and OS. Due to heterogenicity regarding the LRFS, they performed subgroup analysis for which they found no significant disadvantage for PCA in LRFS for cT1a, but they did for cT1b. Furthermore, they concluded that robot-assisted partial nephrectomy could be the most beneficial modality regarding LRFS when compared to PCA. They revealed that for cT1b, PCA was significantly worse compared to PN in terms of both variables, LRFS and OS. No significant difference was found for neither MFS nor CSS.
Nowak et al. concluded that PCA might be a feasible option for patients with T1 renal tumors who also have comorbidities. While also showing the superiority of PN when it comes to the treatment of cT1b renal tumors.(10)
This systematic review and meta-analysis provides a profound overview over PCA and PN but did not include a thorough differentiation between treatment modalities for PN and other methods to perform CA.

5.3 LIU ET ALL. (2024)

A paper which compares partial nephrectomy with cryoablation in general without only focusing on percutaneous cryoablation, was published in 2024 by Liu et al.
Seven studies were included into the systematic review and meta-analysis with a total of 1.400 patients. 1.069 patients (76,4%) underwent PN and 331 patients (23,6%) underwent CA.
The patients undergoing CA had significantly reduced operative time compared to PN, also the estimated blood loss, length of stay and incidence of post-operative complications was significantly lower in the CA group. In terms of transfusion rates, no significant difference was found between PN and CA.
The renal functional outcomes favor CA as well. The increase in serum creatinine levels and the decrease in eGFR was significantly lower in CA compared to after PN.
For the oncological outcomes the local recurrence rate and the distant metastasis rate is presented. For PN the mean follow-up period ranged from 28,7 to 58,6 months while it ranged from 28 to 75,3 months for CA. Liu et al. found no significant difference in neither rate of LR nor DM. (11)
While Liu et. al provide an overview over PN in general over CA without further discrimination between CA techniques, it does not provide a detailed comparison regarding the different partial nephrectomy approaches.

5.4 SYNAPSIS

All three previous mentioned systematic reviews and meta-analyses generally compare partial nephrectomies to focal therapies while not always indicating which exact treatment modalities they assessed. They performed the comparison by assessing various outcomes, such as perioperative outcomes, renal functional outcomes and oncological outcomes. For the perioperative outcomes, they agree that FT shows advantages over PN in terms of shorter operative time, reducing the blood loss, shortening the length of stay, and reducing the complication rates, especially minor complications.
In terms of renal function preservation, there is some controversy. Dong et al. and Liu et al. share the position, that FT is superior in preserving the renal function while Nowak et al. found no significant difference in renal function.
For the oncological outcomes, Nowak et al. noted that for cT1b tumors, PCA might be inferior in terms of LRFS, however, Dong et al. and Liu et al. found no significant difference in LR or DM. (8,10,11)

Table 1 summarizes the three systematic reviews and meta-analyses and show which treatment modality was considered best regarding each variable, as according to the three articles. For instance, the operative time was statistically significant shorter for patients undergoing focal therapies within the publication by Dong et al., this is also reflected by Liu et al. in which cryoablation, which is a focal therapy, show statistically significant shorter operative time compared to partial nephrectomies (8,11). For local recurrence free survival, the publication by Nowak et al. indicated statistically significant difference favoring minimal invasive partial nephrectomy only for cT1b renal rumors, this is the reason why the box within the table states it additionally (10).

These findings have been visualized in the table below where which box indicated the superior treatment method according to the three publications. When there was not a statistically significant difference visible, NS has been stated. An extensive listing of all the abbreviations needed to read the table is indicated within the last row of the table.

Table 1: Presenting favorable approaches according to variables.

Study	*Treatment Modalities*	*OT*	*EBS*	*LOS*	*Transfusion Rates*	*Complications*	*eGFR*	*Creatinine*	*LR*	*DM*	*LRFS*	*OS*	*MFS*	*CSS*
Dong et al. (8)	MIPN vs. FT	FT	FT	FT	NA	FT (Clavien I-II, overall)	FT	NA	NS	NS	NA	NA	NA	NA
Nowak et al. (10)	PN vs. PCA	NA	NA	NA	NA	PCA (overall)	NS	NA	NA	NA	PN (cT1b) MIPN	PN	NS	NS
Liu et al. (11)	PN vs. CA	CA	CA	CA	NS	CA	CA	CA	NS	NS	NA	NA	NA	NA
OT = operative time; EBS = estimated blood loss; LOS = length of stay; eGFR = estimated glomerular filtration rate; LR = local recurrence; DM = distant metastasis; LRFS = local recurrence-free survival; OS = overall survival; MFS = metastasis-free survival; CSS = cancer specific survival; MIPN = minimal invasive partial nephrectomy; FT = focal therapy; PN = partial nephrectomy; PCA = percutaneous cryoablation; CA = cryoablation; NA = not applicable/available; NS = No significant differences														

5.5 LIMITATIONS

All three reviews contain limitations primarily related to heterogeneity among the included studies. Variations in study designs, surgical techniques, and patient selection make direct comparison challenging and limit the strength of the conclusions. Also, none of the reviews offer a detailed comparison between specific surgical techniques, such as RAPN and LPN, or between various CA methods, except the study by Nowak et al. which focused on PCA. Up to my knowledge there is no literature review which focusses on the MIPN (RAPN and LPN) and compares them with CA for T1a and T1b renal cell carcinoma. This thesis aims at contributing to this lack in literature.

6. METHODS

The following chapter will address the methods of retrieving and assessing literature for compatibility.

6.1 INFORMATION SOURCES, SEARCH STRATEGY, AND SELECTION PROCESS

A comprehensive search of the PubMed database was conducted to identify free full literature assessing LPN, RAPN or CA for T1a or T1b renal cell carcinoma which were published within the past 10 years. Publications from 2020 to 2025 were selected and screened for relevance to ensure inclusion of the most recent publications. The search string used free-text terms as well as Boolean operators. Multiple variations and abbreviations of the treatment modalities and the disease were used to ensure wide coverage. The Boolean string used is displayed below in figure 1. This method yielded 111 articles, which were then tried to acquire and if possible, imported into Zotero for further screening. After further review, 11 articles were judged suitable for inclusion in this thesis. Why studies have been excluded is described in the following section.
The selection process can be displayed by using a variation of the PI(C)O framework. The population, which was looked for, was patients with a diagnosis of a T1a or T1b RCC. Excluded were therefore studies in which the patients did not match the P. A total of 61 studies were excluded due to not focusing on the stages T1a or T1b, furthermore some of the excluded studies focused on T1a and T1b but pooled the results and therefore it was not possible to assess the outcomes for each stage separately. Those studies have also been excluded. Additionally, some studies did not assess RCC but other diseases like renal cysts or did focus on RCC but in patients with hereditary RCC diseases, those studies have been excluded as well. For interventions, any of the three treatment modalities was acceptable. Overall, 4 studies have been excluded due to not matching the interventions of interest, but for example assessed the feasibility of Girentuximab for single photon emission computed tomography (12), or assessed highly specific procedures which makes them less comparable to the standard practice across all three treatment modalities (13,14). While this remains interesting for future research, it was judged neglectable when performing baseline comparison between the three treatment modalities. Comparison was not a necessary criterion at this point, but any comparison group was accepted and consequently the intervention was assessed independently from the comparison. Outcomes which were considered acceptable were based on the renal function, data on interventions, or oncological outcomes. Six studies have been excluded due to not providing relevant outcomes. An extensive listing can be seen in the tables within the following sections. It was not necessary, that the outcomes extracted were primary endpoints of the included study, it was sufficient, if they were provided. Overall, 9 studies were excluded since their study design was not appropriate for this thesis, such as systematic reviews and meta-analyses, case series, narrative reviews and trial protocols (15–23). Furthermore, 1 study was excluded since it was not in English and 1 study was not retrievable (24,25). Applying the just explained methods, 11 studies were remaining. An overview

on the selection process is also presented below in figure 2, showing a PRISMA flow chart of the process (26). An overview about the included studies is shown in table 2 below, displaying information on the study design, the number of the patients included in the studies, the procedures which were assessed, the stage of the RCC, as well as the follow-up period. The table has been structured into the first six studies assessing T1a stages while the remaining five assess T1b RCC. Included were mostly retrospective studies and two prospective studies both of which were randomized (27,28).

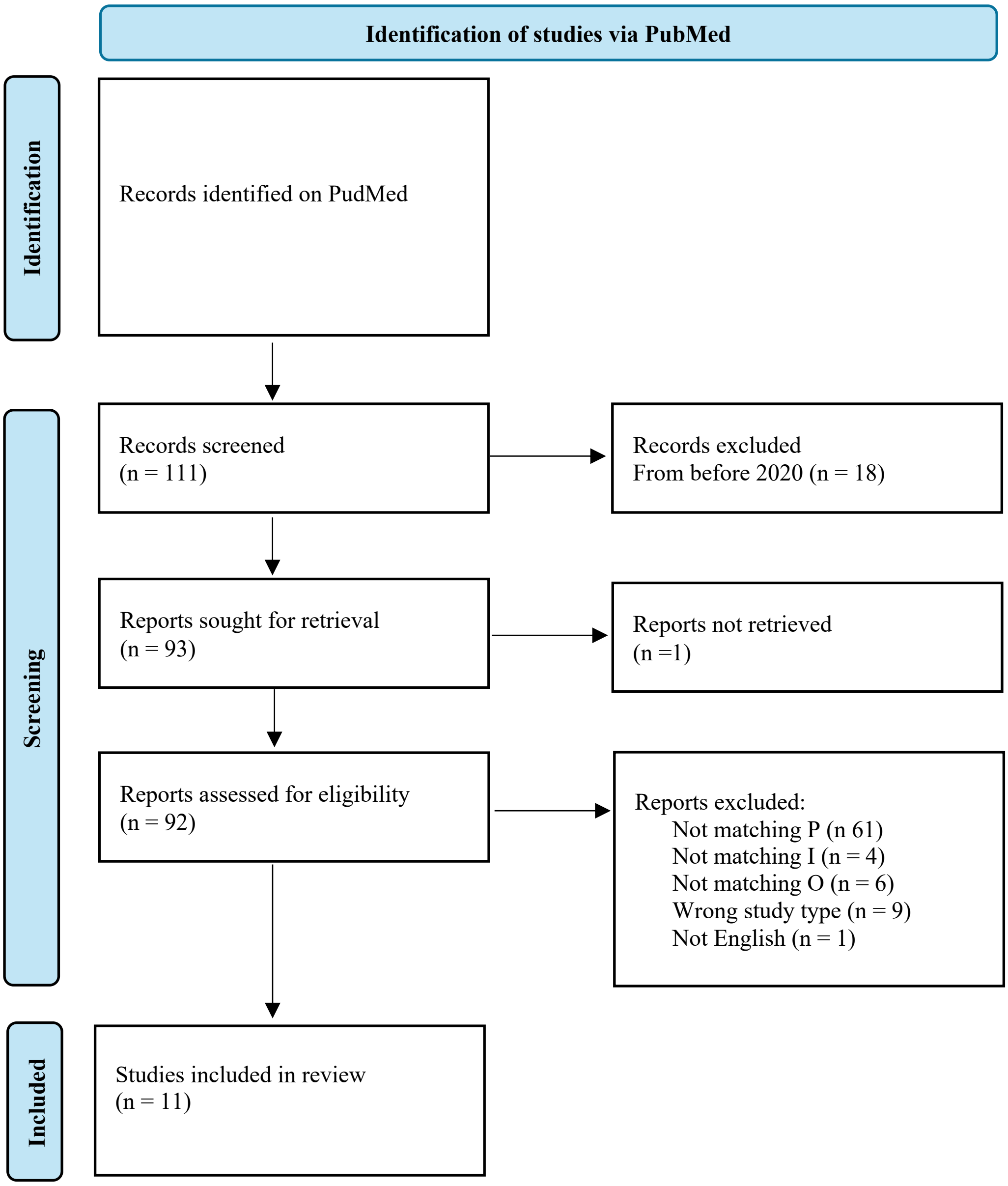
Table 2 – Characteristics of included studies

Study	*Design*	*N*	*Procedure*	*RCC Stage*	*Follow-up period**
Kula (29)	Retrospective comparative	110	MWA, LPN	T1a	2 years
Li (27)	Prospective randomized cohort	99	RAPN	T1a	12 weeks
Chan (30)	Retrospective comparative	296	CA, RFA, LPN	T1a	10 years
Yao (31)	Retrospective cohort	130	LPN	T1a	NA
Fujisaki (32)	Retrospective cohort	50	RAPN	T1a	1 year
Wu (28)	Prospective randomized comparative	183	LMWATE, LPN	T1a	1 year
Yamamoto (33)	Retrospective cohort	50	RAPN	T1b	180 days
Barjolle (34)	Retrospective cohort	63	CA	T1b	3 years
Tang (35)	Retrospective cohort	92	RAPN	T1b	90 days
Yu (36)	Retrospective comparative	146	LPN, LRN	T1b	5 years
Deng (37)	Retrospective comparative	170	LPN, RAPN	T1b	80 months
MWA = microwave ablation; LPW = laparoscopic partial nephrectomy; LRN = laparoscopic radical nephrectomy: LMWATE = laparoscopic microwave ablation assisted tumor enucleation; RAPN = robot-assisted partial nephrectomy; CA = cryoablation; NA = not applicable/available; N = number of patients; * up to the indicated time					

Figure 1 – Boolean string

(("robot-assisted partial nephrectomy" OR "robotic partial nephrectomy" OR "laparoscopic partial nephrectomy" OR "renal cryoablation" OR "kidney cryoablation") AND ("small renal mass" OR "localized renal tumor" OR "stage I renal cell carcinoma" OR "T1a"[Title/Abstract] OR "T1b"[Title/Abstract] OR "renal cell carcinoma" OR "kidney cancer" OR "renal cancer") AND (retrospective[Title/Abstract] OR prospective[Title/Abstract] OR cohort[Title/Abstract])) AND ((y_10[Filter]) AND (ffrft[Filter]))

Figure 2 – PRISMA flowchart for cohort study selection



6.2 DATA COLLECTION PROCESS AND DATA ITEMS

The remaining 11 articles were carefully studied, and relevant data was extracted and put into an excel file for better overview and structuring tables for this thesis. Efforts were made to provide data with any additional information such as the used measure of central tendency, to be more precise mean or median, as well as the units used in the studies. Data was usually present in tables within the articles, but data mentioned within the text was also extracted whenever applicable. Items of interest were information regarding the study itself, whether the study design was retrospective or prospective, country in which the study was carried out, timeframe from which the data originates, number of patients included, treatment modalities, and stage of the RCC. Furthermore, information on the performed procedure in terms of estimated blood loss, preoperative and postoperative hemoglobin, and complications were of interest. Also, functional results like pre and postoperative eGFR and creatinine, as well as oncological outcomes such as follow-up duration, recurrence, cancer specific survival, overall survival, local recurrence and local recurrence-free survival, distant metastasis and metastasis free survival, residual tumor lesion, local tumor progression, and disease-free survival have been included.

7. RESEARCH RESULTS

The data extracted from the previously outlined articles are presented in the following chapter. Two separate sections are provided, one for T1a RCC and one for T1b RCC. Each section is structured in a way, that in the beginning the baseline characteristics of the patients included into the studies are outlined, then data regarding the intervention itself, followed by functional as well as oncological results. A broad overview is established within the text, a more detailed and comprehensible overview is available through the tables, which show the findings as extractable from the articles. Total numbers where applicable were calculated and units are provided where available.

7.1. T1a

7.1.1 PATIENTS BASELINE CHARACTERISTICS

The amount of patients included in each group ranges from 49 (27) to 93 (28), with a total amount of patients within the LPN group of 357 (28–31), within the RAPN group of 163 (27,32) and within the CA group of 72 (30). Across the assessed articles, the age of patients who underwent LPN for T1a tumors ranged from a mean or median of 56 to 59 years of age (28,30,31,38). For RAPN the age spread from a mean of 52.14 years of age to a median of 61 (27,32). Divergent to that, the age of patients undergoing CA was only provided in one study with a median age of 72 years (30). Regarding the sexual distribution, majority of patients of every study were male (27–32). Not every article provided data on body mass index (BMI) of their patients, but of those which did, patients BMIs were between a median of 24.5 and a median of 26 (31,32). Since all studies strictly assessed T1a tumors, all of them were below 4 cm of size but varied within from a median of 2.5 cm to a median of 3.5 (31,32), or classified them as being below 4 cm of size (27). The RENAL/PADUA score was presented either by stating the median with the corresponding IQR, or by stating the % of patients within predefined subgroups. Within the articles stating the median, the lowest was by Chan et al. with a median of 5 and an IQR of 4-7 within the group on LPN (30), and the highest as well in the group on LPN with a PADUA median of 7 and a range of 6-10 by Wu et al. (28). The studies on

RAPN and CA reported a median of 7 and a range of 4-10 by Fujisaki et al. on RAPN (32), and a median of 6 with an IQR of 5-7 by Chan et al. on CA (30).

Table 3 – Patient baseline characteristics T1a

Author	Groups	N	Age (years)	Male n (%)	Female n (%)	Body mass index	Tumor size (cm)	RENAL (PADUA) score
Laparoscopic partial nephrectomy								
Kula (29)	NA	55	56 MA	31 (56)	24 (44)	NA	3 MD	NA
Chan (30)	NA	79	59 MD	52 (65.8)	27 (34.2)	NA	2.5 MD	5 MD
Yao (31)	Lumbar vein used as landmark	73	58.5 MA	55 (75.3)	18 (24.7)	26 MA	3.2 MD	Score 4-6 79.5%, Score 7-9 20.5%
	Lumbar vein not used as landmark	57	56 MA	39 (68.4)	18 (31.6)	25.4 MA	3.5 MD	Score 4-6 73.7%. Score 7-9 26.3%
Wu (28)	NA	93	57 MD	60 (64.5)	33 (35.5)	24.7	3 MD	7 MD,P
(Total)	NA	357	NA	237 (66.4)	120 (33.6)	NA	NA	NA
Robot assisted partial nephrectomy								
Li (27)	KangDuo Surgical Robot	49	54.36 MA	27 (55.1)	22 (44.9)	25.8 MA	<4 (100%)	NA
	Da Vinci Si Surgical System	50	52.14 MA	35 (70)	15 (30)	25.63 MA	<4 (100%)	NA
Fujisaki (32)	NA	50	61 MD	31 (62)	19 (38)	24.5 MD	2.5 MD	7 MD
(Total)	NA	163	NA	102 (62.6)	61 (37.4)	NA	NA	NA
Cryoablation								
Chan (30)	NA	72	72 MD	42 (58.3)	30 (41.7)	NA	2.85 MD	6 MD
(Total)	NA	72	NA	42 (58.3)	30 (41.7)	NA	NA	NA

N = Number of patients; NA = not available/applicable; For Wu BMI it was not indicated if it is median or mean; Tumor size for Li was below 4 cm for 100% of the patients included; P = PADUA; MA = mean; MD = median;

7.1.2 INTERVENTIONAL DATA

For the intervention data, only data regarding LPN as well as RAPN was available in assessed articles. For CRA the assessed articles did not provide data which was matching the inclusion criteria: EBL and complications. One outlier in terms of estimated blood loss was within the group of studies assessing LPN, with a median of 117.5 ml while for all other studies it was a median of 50 ml (28). The postoperative classifications were presented according to the CD classification. The studies by Kula et al., Wu et al., and Li et. al stated the level of complications according to the CD classification with the corresponding % of the amount of patients attributable to each level (27–29). The study by Fujisaki et al. reported the amount of patients as well as the corresponding % for CD complications larger then III (32).

Table 4 – Interventional data T1a

Author	Groups	Estimated blood loss (ml)	Postoperative complications (n and %)
Laparoscopic partial nephrectomy			
Kula (29)	NA	NA	Clavien Dindo I: 1 (17%) Clavien Dindo II: 2 (33%) Clavien Dindo IIIa: 2 (33%) Clavien Dindo IIIb: 1 (17%)
Yao (31)	Lumbar vein used as landmark	50 ^{MD}	NA
	Lumbar vein not used as landmark	50 ^{MD}	NA
Wu (28)	NA	117.5 ^{MD}	Clavien I: 4 (4.3%) Clavien II: 3 (3.2%) Clavien IIIa: 2 (2.2%)
Robot assisted partial nephrectomy			
Li (27)	KangDuo Surgical Robot	NA	Clavien Dindo I: 3 (6.12%)
	Da Vinci Si Surgical System	NA	Clavien Dindo I: 1 (2%) Clavien Dindo II: 2 (4%)
Fujisaki (32)	NA	50 ^{MD}	> Clavien Dindo III: 1 (2%)
EBL = estimated blood loss; Hb = hemoglobin; postoperative Hb meaning the latest available Hb; NA = not available/applicable; ^{MD} = median			

7.1.3 FUNCTIONAL RESULTS

The functional results of studies assessing T1a RCC mainly focused on two parameters, the serum creatinine (sCr) and the eGFR. sCr measured pre and postoperatively was presented by one study for LPN, Kula et al. and showed a decline from a median of 0.8 to a median of 0.76 mg/dl of sCr (29). The eGFR notes a decline across all studies except for the one previously mentioned study by Kula et al. (29), which states a median of 98.3 for both pre and postoperative measuring's, but a change in the range from 36.7-139.3 preoperatively and 51.8-133.3 postoperatively. A detailed overview is given in table 5 which provides a well-structured overview on the functional results following said interventions.

Table 5 – Functional results T1a

Author	Groups	Preoperative serum creatinine (mg/dl)	Latest available serum creatinine (mg/dl)	Preoperative estimated glomerular filtration rate	Latest available estimated glomerular filtration rate
Laparoscopic partial nephrectomy					
Kula (29)	NA	0.8 ^{MD}	0.76 ^{MD}	98.3 ^{MD}	98.3 ^{MD}
Chan (30)	NA	NA	NA	91.31 ^{MD}	75.2 ^{MD}
Wu (28)	NA	NA	NA	102.4 ^{MD}	Change after 12 months -12.5 ^{MD}
Robot assisted partial nephrectomy					
Li (27)	KangDuo Surgical Robot	NA	NA	94 ^{MD}	94 ^{MD}
	Da Vinci Si Surgical System	NA	NA	96 ^{MD}	93 ^{MD}
Fujisaki (32)	NA	NA	NA	74.5 ^{MD}	66.5 ^{MD}
Cryoablation					
Chan	NA	NA	NA	77.88 ^{MD}	68.9 ^{MD}
sCr = serum creatinine; eGFR = estimated glomerular filtration rate; eGFR in mL/; NA = not available/applicable; ^{MD} = median					

7.1.4 ONCOLOGICAL OUTCOMES

Regarding the oncological results, first notable difference is within the follow-up period. While not all studies published the follow-up periods. Those studies which did, differed from a median of 40 months (29), to a median of 75.6 months (30). The study by Chan et al. presented data on the 10 years outcomes, which is above the upper quartile of the presented interquartile range of the follow-up period, and presented their oncological outcomes by percentage and 95% confidence interval (CI) (30). The study by Kula et al. presented the data on residual tumor lesions and local tumor progression by stating the amount of patients within each category and indicating the percentage, as well as stating the disease-free survival in months (29). The results are summarized in table 6 below.

Table 6 – Oncological outcomes T1a

Author	Follow-up duration (months)	Cancer-specific survival (%)	Overall survival (%)	Local recurrence-free survival (%)	Metastasis-free survival (%)	Residual tumor lesion n (%)	Local tumor progression n (%)	Disease free survival (months)
Laparoscopic partial nephrectomy								
Kula (29)	40 MD	NA	NA	NA	NA	3 (5.5%)	1 (1.8%)	62.9 MD
Chan (30)	72 MD	98.7%	87.6%	93.3%	93.3%	NA	NA	NA
Cryoablation								
Chan (30)	75.6 MD	100%	73.9%	92.3%	100%	NA	NA	NA
NA = not available/applicable; MD = median								

7.2 T1b

7.2.1 PATIENTS BASELINE CHARACTERISTICS

The amount of patients included in each group ranges from 14 (30) to 63 (34). With a total of 134 within the group of patients undergoing LPN (30,36,37), a total of 200 undergoing RAPN (33,35,37), and a total of 94 undergoing CA (30,34). The age of the included patients was displayed either by median with interquartile range or by mean with standard deviation. The age distribution for LPN ranged from a mean of 49.77 years (36) to a median of 57 years (39). A similar range can be seen in the group of studies assessing RAPN. Here the range spreads from a mean of 50.5 years (35) to a median of 62 years (33). The group of studies assessing CA displays a remarkable difference regarding their age groups. While the studies compared to each other don´t have major variations in the age range, the age compared to the PN groups differs. For the CA studies the age ranged from a median of 77.0 years (39) to a median of 79.5 years (34). In all except for one group, which assessed LPN and included 42.9% male and 57.14% female patients (30), did the male sex outlie the female sex. Within groups with the majority of patients being of the male sex, distributions varied from 53.4% male and 46.6% female (37) to 82.5% male and 17.5% female (34). Three groups were within 10% to a 50/50 distribution (30,37). For two groups the presented data was only covering the male sex (37). Here the data for the female sex was calculated. The patients body mass index was presented in five out of the nine groups (33–36). The data presented ranges from a mean of 20.3 kg/m2 (35) to a median of 27 (34). The majority of the groups are below a BMI of 25 (33,35,36) with only one group lying over it (34). The outlier group incorporates patients treated with CA (34). Most groups which present the BMI are groups which were treated with RAPN (33,35). Since this section of the thesis focusses on T1b renal cell carcinomas, all included groups only present data for patients with tumors within that size. The range is from a median of 4.4 cm (33) to a mean of 5.59 cm (36). The largest tumor size was in the group of patients undergoing LPN (36), and the smallest in the group undergoing RAPN (33). It is worth mentioning that the group covering CA incorporated patients with a median of 4.5 cm (30,34), being also on the lower end of the spectrum. Seven out of the eight groups which provide RENAL or PADUA score, do so with providing the median with IQR (30,33,37) or mean with SD (35). Within those groups the lowest was a RENAL score median of 7 with an IQR of 5-8 for a group undergoing LPN (30). The highest was a group with a RENAL score mean of 9.2 with a SD of 1.55 for a group undergoing RAPN (35). One of the two groups which underwent CA presents the RENAL score by stating how many patients are contributed to each group from RENAL score 6 to 11, as well as the corresponding % of the overall number of patients within said group (34). In the groups undergoing CA, the one group stating the n as well as the % had the majority of patients with a RENAL score of 9, 18 patients out of 63 making 28.6% (34) and the other group which presented their data for the RENAL score as median with IQR presented a median of 9 with an IQR of 7-10 (30).

Table 6 - Patient baseline characteristics T1b

Author	Groups	N	Age (years)	Male n (%)	Female n (%)	BMI	Tumor size (cm)	RENAL score
Laparoscopic partial nephrectomy								
Chan (30)	NA	14	57 ^{MD}	6 (42.9)	8 (57.14)	NA	4.45 ^{MD}	7 ^{MD}
Yu (36)	NA	62	49.77 ^{MA}	42 (67.74)	20 (32.26)	24.73 ^{MA}	5.59 ^{MA}	NA
Deng (37)	NA	58	50.6 ^{MA}	32 (55.2)	26 (44.8)	NA	4.9 ^{MA}	8 ^{MD}
(Total)	NA	134	NA	80 (59.7)	54 (40.3)	NA	NA	NA
Robot assisted partial nephrectomy								
Yamamoto (33)	NA	50	62 ^{MD}	36 (72)	14 (28)	23.7 ^{MD}	4.4 ^{MD}	8 ^{MD}
Tang (35)	Transabdominal approach	43	50.5 ^{MA}	30 (69.8)	13 (30.2)	20.3 ^{MA}	4.9 ^{MA}	9.2 ^{MA}
	Retroperitoneal approach	49	52.7 ^{MA}	35 (71.4)	14 (28.6)	22.2 ^{MA}	5.3 ^{MA}	8.8 ^{MA}
Deng (37)	NA	58	52 ^{MA}	31 (53.4)	27 (46.6)	NA	5 ^{MA}	8 ^{MD}*
(Total)	NA	200	NA	132 (66)	68 (34)	NA	NA	NA
Cryoablation								
Barjolle (34)	NA	63	79.5 ^{MD}	52 (82.5)	11 (17.5)	27 ^{MD}	4.5 ^{MD}	RS-6: 1 (1.6%) RS-7: 8 (12.7%) RS-8: 15 (23.8%) RS-9: 18 (28.6%) RS-10: 14 (22.2%) RS-11: 7 (11.1%)
Chan (30)	NA	31	77 ^{MD}	22 (71)	9 (29)	NA	4.5 ^{MD}	9 ^{MD}
(Total)	NA	94	NA	74 (78.7)	20 (21.3)	NA	NA	NA
NA = not available/applicable; BMI = body mass index, Tumor size in cm; RS = RENAL score; ^{MD} = median; ^{MA} = mean; * score not indicated								

7.2.2 INTERVENTIONAL DATA

Estimated blood loss is presented in six out of the nine groups (33,35–37). No data is presented for CA. Within the groups which present the EBL, the lowest is in a group undergoing RAPN with a mean of 42.8 ml and a SD of 6.6 (35), and the highest is in a group undergoing LPN with a median of 200 ml and an IQR of 100-300 (37). Overall, all groups undergoing LPN had an EBL higher than 100 ml (36,37), while of the group undergoing RAPN only one was above 100 ml (37), while the remainder were below 100 ml (33,35). Like the data available for EBL, for the postoperative complications, there is not data presented within the groups undergoing CA. The data presented for LPN and RAPN, differs within each treatment modality. One group undergoing LPN states the amount of patients which experienced postoperative complications and the respective % of the amount of patients within this group (36). This is also the case for two groups undergoing RAPN (35). The remaining three groups list the complications using the CD classification and stating the amount as well as the respective % of the overall population within said group (33,37). Overall complications are presented for three groups, one of each treatment modality (34,37). They are presented by stating the number of patients as well as the % of the corresponding group. The lowest overall complication was noted to be in the group undergoing RAPN (37), and the highest in the group undergoing LPN (37).

Table 7 - Interventional data T1b

Author	*Groups*	*Estimated blood loss (ml)*	*Postoperative complications n (%)*
Laparoscopic partial nephrectomy			
Yu (36)	NA	107.94 ^{MA}	6 (9.68%)
Deng (37)	NA	200 ^{MD}	Clavien Dindo 1-2: 13 (22.4%) Clavien Dindo 3-4: 4 (6.9%)
Robot assisted partial nephrectomy			
Yamamoto (33)	NA	83 ^{MD}	≥ Clavien Dindo 3: 2 (4%)
Tang (35)	Transabdominal approach	50.2 ^{MA}	1 (2.3%)
	Retroperitoneal approach	42.8 ^{MA}	1 (2%)
Deng (37)	NA	160 ^{MD}	Clavien Dindo 1-2: 9 (15.5%) Clavien Dindo 3-4: 3 (5.2%)
Cryoablation			
Barjolle (34)	NA	NA	17 (27%)
NA = not available/applicable; ^{MD} = median; ^{MA} = mean;			

7.2.3 FUNCTIONAL RESULTS

Functional results were presented as preoperative eGFR and latest available. The preoperative eGFR ranges from a median of 57.6 with an IQR of 42.8-79.2 in a group undergoing CA (30) as the lowest to a mean of 88.7 with a SD of 14.4 in a group undergoing RAPN (37) as the highest. Correspondingly, the lowest latest available eGFR was in the previously mentioned group undergoing

CA with a median of 56.4 and an IQR of 34.1-77.8 (30), and the highest latest available eGFR in the previously mentioned group undergoing RAPN with a mean of 80.8 and a SD of 14.9 (37).

Table 8 – *Functional results T1b*

Author	*Preoperative* estimated glomerular filtration rate (ml/min/1.73m^2)	*Postoperative* estimated glomerular filtration rate (ml/min/1.73m^2)
Laparoscopic partial nephrectomy		
Chan (30)	84.8 ^{MD}	61.5 ^{MD}
Yu (36)	83.07 ^{MA}	70.49 ^{MA}
Deng (37)	88.5 ^{MA}	77.2 ^{MA}
Robot assisted partial nephrectomy		
Yamamoto (33)	70 ^{MD}	65 ^{MD}
Deng (37)	88.7 ^{MA}	80.8 ^{MA}
Cryoablation		
Chan (30)	57.6 ^{MD}	56.4 ^{MD}
^{MD} = median; ^{MA} = mean;		

7.2.4 ONCOLOGICAL OUTCOMES

Oncological outcomes are presented for four groups, of which two underwent LPN (30,36) and two underwent CA (30,34). For RAPN, no group presented oncological outcomes. Two groups did not present their data with 95% CI (34,36). Two groups presented their follow-up duration as median with IQR (30), and one stated the amount of years with 5 years (36). The remaining group states the oncological outcomes together with the time over which they are recorded - in this case, 3 years for each outcome (34). Cancer specific survival (CSS) was presented for one group undergoing LPN (30), and two groups undergoing CA (30,34). The group undergoing LPN, presented a 100% with a 95% CI being NA over 10 years (30), while the two groups undergoing CA, showed 95.2% over 3 years (34), and 96.4% with a 95% CI of 77.2%-99.5% over 10 years (30). Overall survival (OS) was presented for all four groups (30,34,36). The OS ranged from 43.5% with a 95% CI of 24.5% to 61.9% over 10 years for a group undergoing CA (30) to an OS of 87.3% over 3 years also undergoing CA (34). The groups undergoing LPN were also within that range (30,36). Local recurrence (LR) was only provided for one group, which stated that 11.1% of the patients who underwent CA had a LR over a period of time of 3 years post treatment (34). Distant metastasis (DM) were presented for one group undergoing LPN (36) and one undergoing CA (34). The group undergoing LPN presented 4 patients (6.45%) having DM (36), and the group undergoing CA 11.1% over 3 years (34). Local recurrence-free survival (LRFS) ranges from 46 or 74.19% for a group undergoing LPN (36), to 86.4% with a 95% CI of 61.7% to 95.6% over 10 years of a group undergoing CA (30). Metastasis free survival (MFS) was presented for a group undergoing LPN (30) with a MFS of 100% and a 95% CI of being NA over 10 years and for a group undergoing CA (30) with a MFS of 96.7% and a 95% CI of 78.6% to 99.5% over 10 years.

Table 9 - Oncological outcomes T1b

Author	*Follow-up duration (months)*	*Cancer-specific survival at 3 and 10 yrs (%)*	*Overall survival at 3, 5 and 10 yrs (%)*	*Local recurrence at 3 yrs (%)*	*Distant metastasis at 3 and 5 yrs (%)*	*Local recurrence-free survival at 5 and 10 yrs (%)*	*Metastasis-free survival at 10 yrs (%)*
Laparoscopic partial nephrectomy							
Chan (30)	67.9 ^{MD}	100%	68.1%	NA	NA	74.6%	100%
Yu (36)	60	NA	88.71% ^{5}	NA	6.45% ^{5}	74.19% ^{5}	NA
Cryoablation							
Barjolle (34)	NA	95.2% ^{3}	87.3% ^{3}	11.1%	11.1% ^{3}	NA	NA
Chan (30)	72.5 ^{MD}	96.4%	43.5%	NA	NA	86.4%	96.7%
NA = not available/applicable; ^{MD} = median; ^{MA} = mean; ^{3} = 3 years; ^{5} = 5 years							

8. DISCUSSION

When conducting a literature review authors must skim through many articles and identify those which could be a meaningful contribution for the review. The constantly growing databases give the authors the possibility to access scientific literature at an ease but also make the need for a structured choosing protocol undeniable. One of those protocols which could help the author with this crucial step in conducting a literature review is the PICO framework. This framework guides the author for every single piece of literature and ensures that only those articles, which match the previously stated characteristics are further considered. This has already been described by Schardt et al. in 2007 (40). This approach quickly shows gaps in literature due to its selective nature. The method used in this thesis, Boolean string application in PubMed, also demonstrates the limitations of the availability for literature, when assessing such specific questions. To be more precise, the strict focus on T1a and T1b excluded 73 articles which were not suitable to be used when assessing T1a and T1b RCC. This limitation is also highlighted when revisiting the systematic reviews and meta-analyses stated at the beginning of this thesis. While the article by Nowak et al. assessed T1 in general without further discrimination between the substages, they were also only able to provide 14 studies (10). It is quite clear that if a research topic is as specific as the topic of this thesis is, the amount of available literature becomes thin. One can quickly feel left with only few available articles what may appear as being of poor contribution to the previously stated research question. But it can be argued, that pointing out existing gaps in literature is as itself already a contribution to scientific work, since it points out possible research question for future work (41). Considering this, it can be stated that while the amount of literature incorporated into this thesis is limited to 11 articles (27–37), the literature retrieval is stated transparent and conducted in a tedious matter to ensure that an actual representation on the literature which matches the idea of the thesis is developed.

As stated earlier in this section, a search string which encompasses various terms for the three treatment options as well as various terms for the disease was created. While the initially identified literature encompassed 111 articles only 9.9% of those articles were eventually considered a contribution to this thesis. The amount of literature could have been enlarged by also incorporating studies which were older, but to provide an overview on the current state of research, the limit of the year 2020 was chosen. As previously stated, this was also done to ensure that no studies are already assessed in the incorporated systematic reviews and meta-analyses and are considered new contribution to the scientific literature available. Six studies could be considered cohort studies in which the focus lies on one procedure (27,31–35), and the remaining five incorporated more treatment modalities (28–30,36,37), and could therefore be considered comparative studies. As of best knowledge, there is currently no prospective randomized study directly comparing LPN, RAPN, and CA. Therefore, cohort studies were considered acceptable. Furthermore, the comparative studies were treated as if they were cohort studies. This decision was done since there is no difference in retrospective studies either being cohort or comparative until the comparative statistical methods are performed. Since those are not of interest for this thesis, this decision remains appropriate. It has already been established, that randomized controlled trials create high quality and reliable evidence (42). Unfortunately, it remains challenging for researchers to perform randomized controlled trials, when it comes to invasive treatments for oncological diseases. Ethical considerations should not be neglected when designing a study and for physicians the health of a patient is nothing to be taken lightly. Fortunately, the previously stated databases as well as the digital documentation of most day-to-day practices conducted in health care facilities, enable researchers to conduct retrospective studies which do not influence the treatment plan for any included patient since the treatment has already been performed. Studies generally bear the risk of bias, and this should be considered when reading studies and interpreting results. This also becomes important when working with retrospective studies. Inclusion and exclusion criteria of patients can shape the pool of participants in various directions. Also, for this thesis inclusion as well as exclusion criteria have been used, therefore also for this thesis a selection bias could be considered. This was anticipated by the previously outlined selection protocol and Boolean string. The conclusion on the availability of literature regarding this specific field of interest becomes apparent by assessing the tables depicted in the earlier sections of the thesis. The available literature is sparse and warrants for more research.

Despite the already exhaustive discussed deficiency in available literature, studies were excluded also when only tiny deviations to the inclusion criteria were identified. For example, it was decided to exclude a study even though it included cT1a or cT1b patients, but also included patients with higher pathological T stages going as high as pT3a (43). This decision was made because, the pathological stage is the actual stage of the tumor after excerption and is therefore the one predefining the outcome. Initial treatment plans are often developed based on the clinically staging. While this is the case, the outcomes regardless of functional or oncological should be a representation of the actual stage of the tumor. Another example of applying exclusion criteria was by only including studies with patients who were diagnosed with a renal cell carcinoma. While benign lesions which are excerpted by surgical methods impact the renal function, an oncological outcome can be neglected. It could be argued, that for providing more information regarding the renal function, such lesions could have been incorporated. Since the previously stated and predefined objective was on renal cell carcinoma the exclusion criteria have been consequently carried out. While discussing the entity of the lesion, it must be mentioned that histology was not considered, neither for inclusion nor for exclusion criteria. A retrospective study by Wagener et al. from 2017, showed that there is a significant impact of histology on oncological outcomes. According to them, papillary renal cell carcinoma in non-metastatic states, harbors significantly reduced risks for cancer specific death as compared to clear cell renal cell carcinoma (44). The conducted literature retrieval does simply not include such information in a satisfactory matter. This is the reason why at this point in the discussion it should be mentioned that all the oncological outcomes stated in this thesis must be interpreted while considering the unavailability of information regarding the histology.

The included studies assessing T1a renal cell carcinoma, incorporate a total of 592 patients compared to 428 incorporated in the T1b studies, which is a difference of 17.3%. Furthermore, for both stages, the minority is by far the group which received cryoablation. Within the T1a group, only 72 patients underwent cryoablation, and in the T1b group, only 94. This underrepresentation underlines the limitations for comparing cryoablation with its more invasive counterparts. Authors may face difficulties in recruiting enough patients for the studies to be reliable and representative, especially when conducting prospective studies as outlined previously. Across the studies on T1a which were included in this thesis, the majority presented patient numbers of 50 and above, with one study including as many as 93 patients (38,39,31,28,32,27). On the other hand, one study only includes 14 patients (43), such small sample sizes may distort the results and could therefore be assessed consciously, since they may not be as representative as studies including a larger sample size. Also, for T1b, the difference in the number of patients is quite substantial. The group of patients receiving cryoablation is less than half (34,39) compared to robot assisted partial nephrectomy (33,35,37). The group of cryoablation remains largely underrepresented. Summarizing the previous statements, when conducting studies, it should be ensured that the sample size is of sufficient quantity. There is literature available, guiding researchers to ensure that the sample size used is of sufficient quantity. One such method was described by Kang in his paper from 2021 published in the journal of educational evaluation for health profession. He stated, that it has become a major issue to perform appropriate calculation of sample sizes for research and has therefore shown in his publication, that it is possible to calculate sufficient sample sizes for various statistical tests using the G*Power software (45). Including such methods as standard of practice may lead to studies with sample sizes which appear sufficient. These methods could also be of use for readers of studies. Readers could use the previously stated method, to perform a calculation backwards, granting the possibility to judge for oneself, if the study at hand appears to have included enough patients. Since this practice is a more time-consuming approach, most readers will probably not follow this idea. Underlying once again, the need for researchers to present data with is quantitative satisfactory. One approach to ensure the reader that the number of patients included is reasonable, is by stating that sample size calculation has been conducted while performing the study.

Within the T1a group, the article by Chan et al. from 2022 (39) incorporated patients with a median age of 72 years and an IQR from 62 to 76 undergoing cryoablation. This is a distinguishable difference to the ages of all other studies. Since this was the only article assessing cryoablation for T1a, it restricts the ability to compare the outcomes to other groups which received cryoablation and to the other groups which received different treatment methods. For T1b, the age across the groups which underwent laparoscopic partial nephrectomy or robot-assisted partial nephrectomy are somewhat close, while the age for the cryoablation groups differs tremendously. Age of cryoablation is close to 80 years (30,34) while for the nephrectomies is 50-60 (30,33,35–37). The impact of age on the clinical outcomes of patients with renal cell carcinoma is already known since over a decade. Hupe et al. published a study in 2014 highlighting that clinical outcomes such as metastasis, cancer-specific mortality and overall mortality significantly correlates with age (46). Furthermore, Sun et al. published a study in 2011, focusing on the effect of age on cancer specific mortality in patients with all stages, regardless of the treatment which was chosen and by considering mortality due to other causes. They concluded, that the most considerable effect of age on the cancer specific mortality is for patients affected by stage I RCC (47) Sun et al. have used the TNM staging system from 2002 according to the American Joint Cancer Committee (AJCC) stages, in which stage I corresponds to T1N0M0 (47). The previously mentioned findings not only highlight the limitations of comparing study results from populations with varying ages but furthermore highlight how tremendous the effect of age for low stage RCC is. Coming back to the studies assessing CA, incorporation of patients with a higher age is not surprising. Many factors influence the recommendation for one treatment modality over the other. One of such influences is the renal function.

Serum creatinine has been well recognized as a biochemical marker for renal function and is used to measure the eGFR rate across clinical settings (eGFR) (48). Since creatinine is produced in the body at a rather constant rate, one should expect an increase in serum creatinine if any kidney volume is lost since creatinine is eliminated through the kidney (49). However, one study by Kula et al.(29), focusing on T1a, included in this thesis reported a decline of serum creatinine form a median of 0.80 mg/dl to a median of 0.76 mg/dl. Unfortunately, no other study reported sCr neither in the T1a nor the T1b group. What has been reported though, is the change in eGFR. The study by Li et al. reported a steady eGFR of a median of 94 with a narrowing of the range from 58 – 119 to 63 – 118 for the group which was operated using the KangDuo surgical robot (27). All other studies as well as the group undergoing surgery using the Da Vinci Si surgical robot, incorporated in the T1a group reported a decline in renal function (27–30,32). Within the group of articles on T1b RCC no group reported an increase of renal function following the treatment (30,33,36,37). The paradox findings within the T1a group could be attributed to the time points at which the measurements were performed. A publication by Huang et al. already stated that there is a further decline from 5.20 ml/min/1.73 m2 at 1 year to a decline of 13.35 ml/min/1.73 m2 from the baseline at five years post operative time (50). While this could explain a further decline in renal function, the increase in renal function remains unclear. Up to my knowledge the concept of increase in renal function after treatment which leads to a loss of renal tissue is not described yet. One explanation for the decrease in sCr could be, that since creatinine is not produced specifically in the kidney but rather in the body at a constant range, the decline in sCr could be due to a reduction of creatinine production, just like certain lifestyles can lead to an icrease in sCr while kidney function remains unchanged, this has been extensively studied and described for the supplementally use of creatine often used by athletic individuals (51). Another explanation can be that, decrease in sCr could occur postoperatively due to intraoperative hemodilution masking the actual sCr, mimicking an improvement of renal function. Whether the effect of hemodilution on sCr is enough to cause such a change, also remains unclear. One further explanation could be, that the treated tumor was leading to an obstruction or compression of renal parenchyma, which could theoretically lead to impaired functions. Whether this theoretical idea also occurs in clinical practice and whether the changes could be reversible after the obstruction or compression is removed, remain unclear. What has been described previously is, that optimization in hemodynamics during surgery may lead to an improvement of renal perfusion which could lead to an increase in eGFR postoperatively (52). Nevertheless, the previously stated dynamic in decline should be considered when comparing studies as the time points at which the eGFR is measured might differ remarkably. While the preoperative eGFR within the T1b groups of partial nephrectomies are relatively close to each other, the group undergoing CA demonstrated a preprocedural median eGFR of 57.6, shifting away from the other groups which were ranging from a median of 70 (33) up to a mean of 88.7 (37). Following the physiological changes which occur once one loses his or her renal functional units, either due to disease or, like for this groups, due to destruction or extraction of kidney tissue, the eGFR diminishes further. This reduction is attributable to the loss of renal tissue but as well to the ischemia which may occur during PN (53). Pointing out, that following any kind of treatment in which kidney tissues are damaged there is a possibility for kidney function further deteriorating but also that treatment modalities which use a state of ischemia further attributes to functional loss. Since CA does not use ischemia (54), the loss of renal function due to ischemia of the kidney can be neglected. Theoretically, ischemia related damage could also be further decreased by procedures such as selective arterial clamping or off-clamp approaches for partial nephrectomies. One study by Kumar Singh et al. from 2024 outlined that the renal functional outcome in super-selective embolization does not show a significant difference (55), while one study by Zanoni et al. from 2023 showed an improvement in renal function preservation in off-clamp RAPN compared to traditional hilar clamping (56). These inconsistent statements point out, that future studies assessing less ischemic approaches for partial nephrectomies could be informative and contribute to the individualized treatment for patients. Considering the previous findings regarding the renal function outcomes for cryoablation as well as the existing literature, it appears reasonable that cryoablation could be of interest for patients affected by RCC with already existing renal function loss. This is also reflected by the median of 57.6 eGFR in the CA group treated for T1b RCC (39). While this is remarkable low, the biggest decline in eGFR from preoperative to postoperative for T1b is noted in a group undergoing laparoscopic partial nephrectomy, declining from a median of 84.8 ml/min/1.73 m2 to a median of 61.5 ml/min/1.73 m2 (39). Even though, cryoablation provides the worst postoperative eGFR, it provides the best preservation with a decline of only 1.2 ml/min/1.73 m2. It should be noted at this point, that this finding was only observable in one group since there were not any more groups providing data on that. One recently published systematic review and meta-analysis by Huang et al. from 2025, demonstrated a mean decline of 5.20 ml/min/1.73 m2 at 1 year post operative time (50), which is quite close to the demonstrated decline in the group undergoing cryoablation. Finaly, the functional outcomes should be considered together with the age of the patient as well as with the comorbidities, since those also affect functional outcomes (57).

The distribution across male and female sex within the included articles is remarkable unbalanced. A paper published by Krischak et al. in 2025 concluded that the proportion of the female sex in uro-oncological studies remains underrepresented. For kidney cancer, females only make up for a median of 29% of patients while the actual annual incidence for kidney cancer in females is 36% (58). This underrepresentation is also notable in some studies included in this thesis. While five out of the nine groups on T1a included in this thesis exceed the median of 29% as described by Krischak et al. (58), four groups are still below going as low as 17.5% in one group (34). While an analysis of the SEER database by Aron et al. from 2008, showed that when patient data is adjusted for stage and grade between men and women, the cancer-specific survival of either sex is comparable to each other (59), a systematic review and meta-analysis by Nkemjika et al. published in 2023 showed, that there is a statistical significance in survival outcomes for individuals affected by RCC based on their biological sex. According to Nkemjika et al., regardless of treatment method, females are more likely to be cancer free when compared to men (60). While this is the case, there is still need for proper representation of female patients in studies to match the actual incidence and guide physicians safely to treatment methods suitable for everyone, regardless of sex.

The relationship between BMI and health or disease is of interest in many subjects. For instance, in the field of oncology, many studies have been conducted from which the impact of BMI on the incidence can be appreciated. In 2018, Choi et al. have conducted a re-analyses of dose-response meta-analyses of observational studies in which they considered the impact of the BMI on the incidence of 20 specific cancers, one of which happened to be renal cell carcinoma. They concluded, that there is convincing evidence in the form of data, that there is an association of BMI with RCC (61). Interestingly, while BMI might correlate with the incidence there is also evidence that patients with a lower BMI are not necessarily more likely to achieve better oncological outcomes. One systematic review and meta-analysis by Ong et al. from 2023 concluded, that a higher BMI actually is associated with improved long term oncological outcomes, often referred to as the obesity paradox (62). While Ong et al. considered the relationship between BMI and outcomes for patients undergoing various surgical procedures for RCC but not for patients undergoing CA, a clinical study by Zhou et al. published in 2021 which focused also on ablative methods, concluded that oncological outcomes remain comparable regardless of BMI (63). While this might not be considered an obesity paradox, it at least shows the noninferiority regarding treatment of patients with obesity. For the included studies on T1a the studies which reported the BMI did not report oncological outcomes and for T1b, the study by Yu et al. on LPN presented a mean BMI of 24.73 with distant metastasis of 6.45% after 60 months follow-up compared to a study by Barjolle et al. with a median of 27 BMI and 11.1% of distant metastasis after 36 months (34,36). These two studies do not represent the obesity paradox described earlier. It can be argued that such findings are not surprising since body weight is not the only factor influencing oncological outcomes.

When addressing oncological diseases and discussing their treatment, the oncological outcome is of crucial role. A question many physicians are confronted with by patients facing the diagnosis of cancer, is the question for the prognosis (64). Comparing the oncological outcomes across studies is limited due to the follow-up duration on which the outcomes are based. In the T1a groups the study by Kula et al. presents with a median follow-up duration of 40 months and correspondingly with a local tumor progression of only 1.8% (29), a study in the T1b group by Barjolle et al. presented data like overall survival of 87.3% but only for 3 years post operative surveillance (34). Such findings should be considered by also assessing the follow-up duration, since good oncological outcomes with only short follow-up durations miss recurrences or metastasis occurring at a later point. The concept of late recurrences in patients with RCC has already been described in the past (65). Impressive follow-up duration was presented by a study by Chan et al. which focused on both T1a and T1b and presented their oncological outcomes for 10 years after treatment (39). Across said data, which could be considered more meaningful since it covers a longer time frame, one can clearly see data both favoring LPN for T1b RCC and data favoring CRA for T1a RCC. Interestingly, as opposed to the findings by Chan et al., a systematic review and meta-analysis by Klatte et al. from 2013, showed worse outcomes for patients undergoing cryoablation for SRMs (66). Comparing oncological outcomes remains challenging, since often parameters are assessed at varying post operative times, like what has been observed earlier regarding the renal functional outcomes. Regarding T1a, Chan et al. display superior cancer specific survival with a 100%, for cryoablation (30) highlighting that there are patient populations which would profit from such treatments. The guidelines on treatment for renal cell carcinoma by the European Association of Urology also state, that for T1a the oncological outcomes can be favorable for patients treated with cryoablation (7). For T1b cryoablation does not impress with superior oncological outcomes. Here one study by Chan et al. presents laparoscopic partial nephrectomy as superior with a cancer specific survival of 100% (30). This is represented in the previously mentioned guidelines which also states that the method of choice for T1 in general is partial nephrectomy without further separating between T1a and T1b (7). Considering the previously stated findings it can be argued that while PN remains the method of choice for T1 in general, especially for T1a cryoablation could be a valuable method for patients which may not be considered eligible to undergo partial nephrectomy.

Different countries or organizations prefer different item sets for staging or comparing various aspects of patients. In the articles chosen, the reader is confronted with two scoring systems. The RENAL score system and the PADUA score system. According to an article by Dubeux et al. (67), the RENAL and PADUA scoring systems are comparable especially concerning warm ischemia time and postoperative complications. According to Dubeux et al. (67), the RENAL score is sufficient to be applied also for risk stratification for postoperative complications after cryoablation. Whether this also applies for the PADUA score remains unclear. It remains obvious that predicting the likelihood of complications as well as risk stratification is a key element in management of patients. Fortunately, the studies included in this thesis which assessed T1a RCC, were of somewhat similar RENAL or PADUA scores making them in this instance also comparable.

The section of intervention data concerning T1a is lacking any data for CA. Of all the screened articles which were considered applicable for this thesis, not even one provided data on EBL, pre and postinterventional hemoglobin value, or any kind of complications for patients undergoing cryoablation for T1a RCC. It is clear, that it is necessary to incorporate such findings in any well proven guidelines to provide sufficient knowledge for the treating physicians as well as information for collective consensus in treatment planning for the patients. This once again highlights the spare available literature when it comes to said treatment for T1a RCC.

Low rates of complications play a crucial role in patient satisfaction and disease control. Physician should be aware of rates of complications for certain interventions just as for side effects of drugs. Different classifications systems and focus on different complications makes it more difficult to compare studies and find a consensus, just as stated previously for the RENAL and PADUA scoring systems. The EBL was included for two groups undergoing LPN and four groups undergoing RAPN. For the groups undergoing CA, no EBL was provided. There is no obvious superiority of one treatment option over the other since for both treatment options the EBL goes as high as a median of 200 ml (37) for LPN and a median of 160 ml for RAPN (37). But it should be mentioned that within the groups undergoing RAPN the estimated blood loss goes as low as means of 42.8 ml and 50.2 ml (35). This largely correlates with findings already published in articles. One study published by Kubota et al. in 2022, already demonstrated the non-inferiority of RAPN over LPN for clinical T1-2 renal tumors both including cortical renorrhaphy omission (68). Or by a recent published observational study from 2025 by Zuo et al. in which they observed less intraoperative blood loss in patients undergoing RAPN over those patients undergoing LPN for clinical T1a and T1b renal tumors (69). While unfortunately, the included studies don´t demonstrate data on EBL for cryoablation. One systematic review and meta-analysis by Klatte et al. published in 2014, already showed a superiority of laparoscopic CA when it comes to a lower EBL compared to both laparoscopic and robot assisted partial nephrectomy (66). Even though this data exists, establishment of RAPN in more and more clinical facilities, and the age of the just stated publication, might grant for an updated review concerning this matter. Undeniable is the influence of ischemia on renal function, which has been extensively discussed previously in this section. But at this point it should be repeated that ischemia in cryoablation is of no concern.

Complications are presented in an unstructured not comparable matter. While three of the groups provide their postoperative complications by using the Clavien-Dindo classification, three other groups fail to do so, only stating their absolute numbers and the corresponding percentages. Again. CA does not state any postoperative complications. One could argue that there is need to introduce a standard for reporting postoperative complications in studies such as the CD classification and there is supportive data for that. One paper by Clavien et al., going as back as 2009, already demonstrated that the CD classification is sufficient and ready to be established for providing information on postoperative complications (70). One recent publication by Abbassi et al. from 2024, criticized the incorrect implementation of the CD classification, highlighting the need for further standardization when it comes to reporting post operative complications (71). While the CD classification was developed for reporting postoperative complications in surgical procedures (70), the proper implementation for reporting complications in ablative methods remains unclear. While there are some studies implementing the CD classification also for reporting of postoperative complications for CA (72), it appears to be a less established practice, which makes comparing the treatment modalities in a comprehensive matter which does not only focus on long term oncological outcomes but also on the shorter scale post operative complications which remain an important aspect on long-term survival, as described by Pucher et al. in 2014 (73), challenging.

9. CONCLUSIONS AND PRACTICAL RECOMMENDATIONS

Treating oncological diseases is a complex and challenging matter in the field of medicine. The ongoing development in surgical methods, the constant research regarding oncological entities and the ongoing change in demographic variable warrant the physician to stay ahead of development to ensure treatment by best methods possible. This thesis revealed the complex impact of patient related factors on outcomes regarding the renal function as well as oncological. To conclude whether one treatment is superior to the other is simply not possible by the included literature. A narrative approach has been chosen to present findings and highlights peculiarities. Such peculiarities are for instance the reduced reduction in renal function for patients undergoing cryoablation. This finding, if properly studied, could contribute to the providing of individualized treatment methods for patients suffering from T1a or T1b renal cell carcinoma with already diminished renal function, eventually also maintaining the remaining renal function. Such recommendations should be considered carefully and only considered with other important outcomes such as the oncological development after treatment. What has already been described in literature and discussed in the population is the underrepresentation of the female sex in medical studies. This historic exclusion appears to be continued in the included articles. As described earlier, the incidence of renal cell carcinoma in men outweighs the incidence in women. This should not be considered an approval for exclusion of females in studies on renal cell carcinoma, but rather a motivation to include more females in those studies. Furthermore, this thesis shows how difficult different scoring systems as well as different values in the form of mean or median can be when one tries to compare findings across various pieces of literature. What would be favorable is a more uniform approach in which existing scoring systems are used. During the work for this thesis, it came to notice, that while the scoring systems such as the RENAL or PADUA score have been well established and are widely accepted, their usage is less implemented into practice. Incorporating those into both clinical work and then research would be favorable. The development of such should be welcomed and implemented in research modalities. To conclude, literature concerning laparoscopic partial nephrectomy, robot assisted partial nephrectomy, and cryoablation for treatment of T1a and T1b is available. 111 articles were identifiable and incorporate many interesting findings as well as meaningful contributions to medical guidelines but the reduction to only 11 incorporated into this thesis, due to strict inclusion and exclusion criteria, shows significantly the sparse reality of the originally identified 111 articles. We are still in need for future research incorporating more treatment modalities and more patients depicting an actual representation of the population. To conclude which treatment option may be feasible for which patient it can be argued, that partial nephrectomies remain gold standard for patients with more advanced and anatomical challenging tumors, while cryoablation appears as a valid alternative for smaller tumors like T1a and especially for patients having to many comorbidities making them not ideal patients to undergo partial nephrectomy.

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11. ANNEXES

Annex 1: Search string for PubMed:

“(("robot-assisted partial nephrectomy" OR "robotic partial nephrectomy" OR "laparoscopic partial nephrectomy" OR "renal cryoablation" OR "kidney cryoablation") AND ("small renal mass" OR "localized renal tumor" OR "stage I renal cell carcinoma" OR "T1a"[Title/Abstract] OR "T1b"[Title/Abstract] OR "renal cell carcinoma" OR "kidney cancer" OR "renal cancer") AND (retrospective[Title/Abstract] OR prospective[Title/Abstract] OR cohort[Title/Abstract])) AND ((y_10[Filter]) AND (ffrft[Filter]))”.)

Annex 2: PICOS framework

P: Patients with clinical stage T1 renal tumors

I: Treatment with LPN or RAPN

C: Treatment with Cryoablation

O: Perioperative, renal function, and oncological outcomes

S: Retrospective and prospective studies