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KIDNEY DISEASES (G CIANCIO, SECTION EDITOR)

Trends in Surgical Management of T1 Renal Cell Carcinoma

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Abstract Historically, open radical nephrectomy (ORN) represented the standard of care for localized renal cell carcinoma (RCC). While the incidence of T1 RCC is rising, treatment options are developing fast and the standard of care according to European and American guidelines has changed to partial nephrectomy (PN), or laparoscopic radical nephrectomy in patients not suitable for PN. To assess the implementation of guideline recommendations and to profile recent surgical and technical innovations, we reviewed the current literature. We observed that ORN still represents the most commonly used treatment in T1 RCC patients. Utilization of PN increased over time but implementation is still in progress. Whereas PN is frequently used in tertiary care centers, population-based studies suggest discrepancies in the diffusion of standard of care treatments. Alternative minimally invasive approaches for PN are available but their superiority is not yet proven. Further efforts in improving the training of urologic surgeons are required to continue the implementation of guideline recommendations.

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Introduction

Surgical management is associated with a reduction in cancer specific mortality in patients with T1 renal cell carcinoma (RCC) compared to observation [1]. Improvements and increased use of imaging techniques lead to a rising incidence of RCC with a downward stage migration and an increased number of T1 RCC patients [2, 3••]. Simultaneously, novel surgical techniques such as partial nephrectomy (PN) and minimally invasive techniques have evolved tremendously and represent an alternative to open radical nephrectomy (ORN). In fact, PN has been shown to provide improved renal function, lower rates of chronic kidney disease [4, 5], fewer cardiovascular events [6] and comparable oncological outcomes, relative to radical nephrectomy (RN) [4, 5, 7–11, 12••, 13–15]. Moreover, laparoscopic radical nephrectomy (LRN) has been shown to provide equal oncological outcomes [16–18] and lower perioperative morbidity [17–19] compared to ORN. As a consequence, according to current guidelines from the European Association of Urology (EAU) [20] and the American Urologic Association (AUA) [21], PN has become the standard of care for T1 RCC patients and should

be performed whenever possible. If a PN is not feasible, a LRN should be the alternative.

Despite explicit guideline recommendations [20, 21], and even consideration as malpractice [22], ORN remains the most widely used treatment in the management of T1 RCC. In the United States (US), even in patients harboring tumors of 4 cm or less (T1a), up to 66 % were treated with ORN in 2005. Between 1988 and 2005, a majority of patients (78.3 %) received ORN whereas 4.1 % were treated by LRN, 16.4 % were treated by open partial nephrectomy (OPN), and 1.3 % were treated by laparoscopic partial nephrectomy (LPN). [23••] Knowing this data, we hypothesize that there is an underuse of current guideline conform treatments such as PN or minimally invasive nephrectomies. In this review we focus on the spread of nephron-sparing and minimally invasive nephrectomy among T1 RCC patients and highlight potential reasons for their underuse in the urologic community.

Radical Nephrectomy

At present, RN–preferably performed via the laparoscopic approach–is only recommended in the treatment of T1 RCC when PN is not feasible [20]. However, ORN represented the predominant treatment even among North American RCC patients treated for tumors sized 4 cm or less between 1988 and 2005. For those patients with the smallest renal masses, the authors observed a decrease in the utilization of ORN during this time period, from 89 % in 1988 to 66 % in 2005. At the same time, utilization of LRN increased to a peak of 6 % in 2000 and decreased moderately to 4 % in 2005 [23••]. Intuitively, in patients harboring T1b RCC, rates of RN are even higher and range from 89.6 % to 96.6 % in population-based studies (Table 1) [24, 26, 31•]. In general, for patients harboring T1 RCC, the rate of RN in population-based studies decreased over time [24–26, 31•, 33], but remains high with still 63.4 % in 2008 [31•]. Unfortunately, the authors did not differentiate between LRN and ORN, so that currently, evidence on the nationwide use of LRN relative to ORN and PN for T1 RCC patients after 2005 is sparse. The American Board of Urology (ABU) records all renal surgeries, not considering the underlying treatment indication, (e.g. tumor nephrectomy for any stage, renal transplant). According to this dataset, the rate of ORN decreased from 54 % (2002) to 29 % (2010) [35]. Regarding a population-based study on T1a RCC patients (1988–2005), 5 % of all RN were performed laparoscopically [23••]. In contrast, within T1 RCC patients undergoing nephrectomy at Memorial Sloan-Kettering Cancer Center between 2000 and 2007, 15.4 % were performed via the laparoscopic approach [12••].

Reasons for the excessive use of ORN are severalfold. First, as shown for other uro-oncologic procedures, laparoscopic surgery requires special equipment, which is more costly, compared to open surgery [36]. Second, laparoscopic or nephron-sparing surgery requires special training and surgical skills, which might not be universally available. Third, laparoscopic access to the kidney is not possible or reasonable in every patient, due to medical conditions such as polycystic kidneys, history of extensive abdominal surgery, non-tolerance to pneumoperitoneum, difficult retraction, bleeding, failure to progress, and difficult access [37].

However, these arguments cannot fully explain the excessive use of ORN in T1 RCC patients, which does not conform to the widely accepted guideline recommendations. Accordingly, there still is an overuse of ORN in the urologic community, relative to LRN and-even more important-relative to PN.

Partial Nephrectomy

PN currently represents the standard of care for T1 RCC patients [20]. Following population-based studies, the rates of PN in the US for T1 RCC patients increased from 9.6 % [24] (1988–2001), over 15.9 % [26] (1989–2004), and 27.1 % [31•] (1998–2008), to 31.2 % [33] (2000–2008). In 2008, 36.6 % of all T1 RCC patients who underwent nephrectomy were treated with PN [31•]. Intuitively, the likelihood of receiving PN compared to RN increases with decreasing tumor size and tumor complexity. Accordingly, for T1a RCC patients, the rates of PN in population based studies (Table 1) varied from 15.2 % to 37.9 %, with an increase from 4.8 % (1988) to 49.4 % (2008). In contrast, only 3.4 % to 10.4 % of all patients with T1b RCC patients were treated with PN in the community setting [24, 26, 31•],

Kutikov et al. [38] showed that the probability to receive PN was significantly associated with tumor complexity, as quantified by the R.E.N.A.L. (radius, exophytic/endophytic properties, nearness of tumor to the collecting system or sinus in millimeters, anterior/posterior and location relative to polar lines) score. Specifically, patients with a respectively low, moderate or high R.E.N.A.L. score, indicating low, moderate or high tumor complexity, received PN in 88.9 %, 84.2 % and 31.9 % of all cases, respectively [38]. These results were confirmed by Canter et al. [39••] who observed that patients with a low R.E.N.A.L. score were more likely to receive PN (94 %) compared to their high R.E.N.A.L. score counterparts (34 %).

In general, the diffusion of PN in daily practice advanced more rapidly in high volume, teaching and tertiary care centers. Regarding data from tertiary care centers the rate of PN among T1 RCC patients increased from 37.8 % (1987–2007) [28] to 56 % (2000–2007) [12••].

Stratified for tumor size, up to 51.4 % and 20.5 % of all patients with T1a and T1b tumors treated in six European tertiary centers between 1987–2007 [28] were treated with PN. According to data from North American centers, between 2000 and 2007, the rates of PN increased from 69 % up to

Table 1 Observational and institutional databases–analyzed for surgical technique used in T1 RCC patients

Author	Database	Time period	Patients n	PN (%)	RN (%)	OPN (%)	LPN (%)	ORN (%)	cpi
Miller et al. 2006 [24]	SEER	1988–2001	14,647 (T1)	9.6	90.4	*	*	*	*
			7,679 (T1a)	15.2	84.8				
			6,968 (T1b)	3.4	96.6				
Hollenbeck et al. 2006 [25]	NIS	1988–2002	66,621 (RCC, T?)	7.5	92.5	*	*	*	*
Baillargeon-Gagne et al. 2009 [26]	SEER	1989–2004	16,047 (T1)	15.9	84.1	*	*	*	*
			9,524 (T1a)	22.8	77.2				
			6,523 (T1b)	5.7	94.3				
Sun et al. 2012 [27]	SEER/Medicare	1988–2005	6,024 (T1a)	17.7	82.3	*	*	*	*
Bianchi et al. 2013 [23••]	SEER/Medicare	1988–2005	6,024 (T1a)	17.7	82.3	16.4	1.3	78.3	4.1
		1988				7.0	*	89.0	*
		2005				29.0	1.9	66.0	4.0
Zini et al. 2009 [28]	Multi-institutional from tertiary care centers	1987–2007	1,560 (T1)	37.8	62.2	*	*	*	*
			871 (T1a)	51.4	48.6				
			689 (T1b)	20.5	79.5				
Sun et al. 2012 [3••]	SEER	1988–2008	23,671 (T1a)	37.9	62.1	*	*	*	*
		1988		4.8	95.2				
		1988–2002		25.2	74.8				
		2003–2005		39.7	60.3				
		2006–2007		44.8	55.2				
		2008		49.4	50.6				
Smaldone et al. 2012 [29]	SEER/Medicare	1995–2007	5,496 (T1a)	30.3	69.7	*	*	*	*
Gill et al. 2007 [30]	Multi-institutional Cleveland Clinic Johns Hopkins Mayo Clinic	1998–2005	1,800 (T1)	*	*	57.2	42.8	*	*
Thompson et al. 2009 [10]	Multi-institutional Mayo Clinic MSKCC	1989–2006	1,159 (T1b)	25.0	75.0	*	*	*	*
Yang et al. 2012 [31•]	SEER	1998–2008	42,004 (T1)	27.1	72.9	*	*	*	*
		2008	26,400 (T1a)	37.0	63.0				
			15,604 (T1b)	10.4	89.6				
			* (T1)	36.6	63.4				
Dulabon et al. 2010 [32]	SEER	1999–2006	18,330 (T1a)	35.0	65.0	*	*	*	*
Thompson et al. 2009 [12••]	Institutional MSKCC	2000–2007	1,533 (T1)	56.0	44.0	49.1	6.6	37.5	6.8
		2000	* (T1a) / (T1b)	69.0 / 20.0	31.0 / 80.0				
		2007	* (T1a) / (T1b)	89.0 / 60.0	11.0 / 40.0				
Small et al. 2012 [33]	NCDB	2000–2008	125,687 (T1)	31.2	68.8	*	*	*	*
Patel et al. 2013 [34•]	Maryland HSCRC	2000–2011	13,893 (RCC, T?)	18.9	81.1	*	*	*	*
		2000		8.6	91.0	*	0.2	87.0	4.0
		2011		27.0	73.0	11.0	15.7	54.0	19. 0
		2006		*	*	*	*	*	20.0
		2006–2011		*	*	*	*	*	26.0
Poon et al. 2013 [35]	ABU	2002–2010	48,384 **	24.6	75.4	14.7	9.9	36.5	38.9

PN: Partial Nephrectomy, RN: Radical Nephrectomy, OPN: Open Partial Nephrectomy, LPN: Laparoscopic Partial Nephrectomy, ORN: Open Radical Nephrectomy, LRN: Laparoscopic Radical Nephrectomy, SEER: Surveillance, Epidemiology and End Result database, *: not stated, NIS: National Inpatient Sample, T?: T stage unknown, RCC: Renal Cell Carcinoma, MSKCC: Memorial Sloan-Kattering Cancer Center, NCDB: National Cancer Database, HSCRC: Health Service Cost Review Commission, RAPN: Robotic-Assisted Partial Nephrectomy, RARN: Robotic-Assisted Radical Nephrectomy ABU: American Board of Urology, **: Nephrectomy patients with unknown T stage and not exclusively oncologic treatment indication (e.g. donor nephrectomy)

89 % in patients with T1a RCC, and from 20 % to 60 % in patients harboring T1b RCC [12••].

Only few studies separately report rates of OPN vs. LPN. For example, Bianchi et al. reported that within T1a RCC patients treated with PN, 92.7 % underwent OPN (1988–2005). In this population based study, the usage of OPN within all T1a RCC patients increased from 7 % to 29 % [23••]. Analyzing case logs from certified urologists, not considering the underlying treatment indication, Poon et al. reported a 41.2 % OPN rate in 2011 in patients treated with PN [35].

Regarding T1 RCC patients treated with PN, the rate of an open approach ranged between 57.2 % [30] in a multi-institutional series and 88.1 % [12••] in a single center experience from Memorial Sloan-Kettering Cancer Center.

LPN is technically more challenging compared to OPN [20] but has shown excellent perioperative outcomes in experienced hands, providing comparable oncologic and survival outcomes [30, 40–42]. Although, compared to OPN, renal damage is potentially more pronounced, due to warm ischaemia, a longer ischaemia time and longer OP time [41, 42], renal function after LPN seems to be comparable after a follow-up of 3.6 years [42]. More prospective long-term-and ideally randomized-data are warranted to evaluate the impact of LPN on renal function and survival compared to OPN.

According to a population-based study (1988–2005), the LPN rate within T1a RCC patients treated with PN was 7.3 %, whereas the proportion of LPN usage overall T1a RCC patients was 1.3 % and remained low throughout the study period with 1.9 % in 2005 [23••]. The usage of LPN was more frequent in tertiary care centers. Here, the rate of LPN within all T1 RCC patients was 6.6 %, whereas, within patients treated with PN, the ratio ranged between 11.9 % and 42.8 % [30].

In an observational study including patients harboring benign and malignant kidney tumors of any size and stage, an increase in the use of LPN from 2 % (2002) to 17 % (2010) has been observed. Here, the rate of LPN within the patients treated with PN was 40.2 % [35]. To summarize, in the urological community PN is underutilized, especially in non-academic, non-teaching hospitals [23••, 24, 25, 43]. Recent data suggest that at present, LPN remains a treatment alternative in the management of selected patients with easy accessible, preferably exophytic T1 RCC, treated at high volume laparoscopic centers and academic or teaching institutions.

Reasons for the slow implementation of PN are most likely multifactorial. First, PN represents a technically more challenging procedure compared to RN and might, therefore, be avoided by surgeons less well trained during their medical education or with a lower annual case load. A second hypothesis is that, in non-academic and non-teaching hospitals, the beneficial impact of PN on renal outcomes and OS compared to RN might be less appreciated [43]. Third, it has been shown that in the US, certain sociodemographic and socioeconomic factors determine the access to the standard of care in T1 RCC patients. For example, younger age, male gender, Caucasian, married status, more recent year of diagnosis [3••, 23••, 34•, 44], as well as higher income and private insurance [33], predispose patients for PN. In contrast, is has been shown that black females were 47 % less likely to receive PN compared to their male and white counterparts [45].

New Techniques

Minimally invasive treatment options in the context of nephrectomy include traditional laparoscopic nephrectomy, as well as more recent approaches such as laparoendoscopic single-site surgery (LESS), robot-assisted surgery and natural orifice transluminal endoscopic surgery (NOTES).

Laparoendoscopic Single-Site Surgery

LESS is performed by one single skin incision for the introduction of camera and instruments [46]. The first laparoendoscopic single-site surgery radical nephrectomy (LESS-RN) was performed in 2008 [47] and feasibility of LESS-RN has been confirmed [48] with a main advantage in cosmetic outcomes.

Based on the novelty of that technique, no observational data are available but several smaller studies exist, comparing LESS-RN and LRN, suggesting both approaches to be equal in terms of operative complications, estimated blood loss and warm ischaemia time (WIT). LESS-RN patients might be associated with reduced postoperative pain, shorter length of stay (LOS), shorter recovery time and better cosmetic results but also with longer operative time and higher rates of conversion to open nephrectomy compared to LRN [49–59].

Laparoendoscopic single-site surgery partial nephrectomy (LESS-PN) is a challenging technique which is used only in few centers and published experience is sparse. According to the EAU guidelines, LESS-PN can provide an alternative approach in experienced hands but currently it is recommended only as part of clinical studies [60].

Robot-Assisted Nephrectomy

Robot-assisted radical nephrectomy (RARN) was introduced in 2000 [61]; the limited benefit of that approach compared to LRN [62–65] slowed its diffusion into clinical routine and robotic assistance is considered a technical overtreatment for RNs by some authors [60]. However, Patel et al. reported that RARN represented 21 % of all minimally invasive RN performed in the state of Maryland in 2011 [34•].

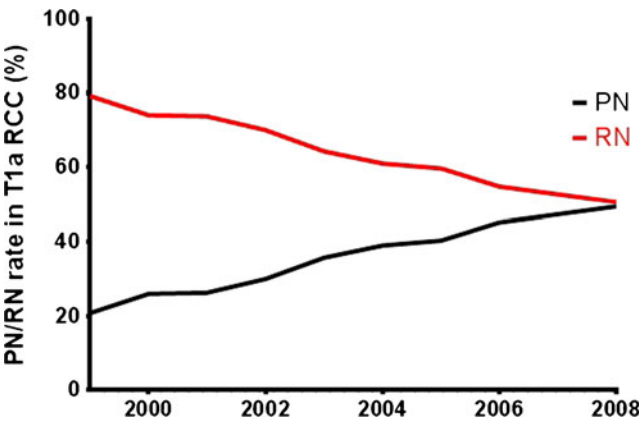

Fig. 1 The rates of PN vs. RN (modified after [32])

Robot-assisted partial nephrectomy (RAPN), introduced in 2004 [66], represents a feasible [60] alternative to OPN or LPN [20]. According to recent data from the Nationwide Inpatient Sample (NIS), within patients treated with minimally invasive PN, RAPN is up to supplant LPN with a utilization rate of 72.5 % vs. 27.5 %, respectively (2008 and 2009) [67]. Furthermore Patel et al. reported that RAPN represented the predominant approach (76.4 %) within RCC patients treated with minimally invasive PN in the state of Maryland 2011 [34•].

However, when comparing RAPN vs. LPN, perioperative outcome seems to be equal for estimated glomerular filtration rate, estimated blood loss, transfusion rate, LOS, OP time and intra- and postoperative complications [67–84]. Whereas four studies reported about an equal warm ischaemia time (WIT) [69, 73, 75, 81], nine studies pointed out an advantage for RAPN in terms of WIT [71, 72, 74, 76, 78–80, 82, 83]. Whereas outcomes of RAPN are not clearly superior relative to LPN, the robotic approach is definitely associated with higher costs [85]. Accordingly, economic considerations, including direct and indirect costs, need to be opposed to long term oncologic and functional outcomes in order to clarify the role of RAPN in the management of T1 RCC patients.

Combining the robotic technique with LESS, the R-LESS approach was first described for urologic surgery in 2009 [86]. In a worldwide multi-institutional series of 1,076 LESS cases, R-LESS was used in 13 % of all LESS procedures for urologic surgery [59]. Although R-LESS has the potential to play a major role in LESS surgery [60], the importance for kidney surgery is currently unclear.

Natural Orifice Transluminal Endoscopic Surgery

Feasibility of NOTES was first demonstrated in 2002 by transvaginal LRN in a porcine model [87]. Whereas the initial NOTES LRN was performed in a hybrid technique with an additional umbilical trocar, the first pure NOTES LRN was reported in 2010 [88]. Although an improvement of patient outcomes was anticipated, the implementation of NOTES struggled with a lack of specific instruments and NOTES remains with limited application these days [89].

Conclusions

In contrast to current treatment recommendations, ORN remains the predominant treatment approach for T1 RCC and the use of LRN remains low. Despite an encouraging increase of PN rates among T1 RCC patients, we observed an overuse of RN (Figure 1), unnecessarily exposing many patients to an increased risk of renal failure. Higher rates of PN in a current series of T1 RCC patients in tertiary care centers reflect disparities in the practice pattern across the urologic community. Several sociodemographic and socioeconomic factors preclude some patients from access to standard of care treatments.

Whereas alternative approaches like LPN, RAPN and LESS-PN are evolving, potential benefits relative to the current standard of care OPN need to be confirmed in well-designed prospective trials. Utilization of novel minimally invasive techniques should not undermine considerations of nephron-sparing surgery. Recognizing, that observational data are always delayed and, therefore, do not reflect current treatment patterns, the described trends need to be confirmed in future studies. Raising the awareness of the benefits of minimally invasive and nephron-sparing approaches in renal surgery as well as systematic training of urologic surgeons might represent important efforts in order to expedite the implementation of guideline recommendations.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Jonas Schiffmann, Dr. Marco Bianchi, Dr. Maxine Sun, and Dr. Andreas Becker each declare no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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