European temporal trends in the use of lymph node dissection in patients with renal cancer

Umberto Capitanio[1,2], Grant D Stewart[3,#], Alessandro Larcher[1,2], Idir Ouzaid[4], Bulent Akdogan[5], Marco Roscigno[6], Martin Marszalek[7], Paolo Dell'Oglio[1,2], Maciej Salagierski[8], Alessandro Volpe[9], Maria Carmen Mir[10], Maximilian Kriegmair[11], Carlo Terrone[9,*], Sabine D Brookman-May[12], Francesco Montorsi[1,2], Tobias Klatte[13]

On behalf of the Kidney Cancer Working Group of the Young Academic Urologists (YAU) Working Party of the European Association of Urology (EAU)

[1]Unit of Urology, University Vita-Salute, San Raffaele Scientific Institute, Milan, Italy
[2]Division of Experimental Oncology, URI, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy
[3]Edinburgh Urological Cancer Group, University of Edinburgh, Western General Hospital, Edinburgh, UK
[4]Bichat University Hospital
[5]Hacettepe University, Ankara, Turkey
[6]Papa Giovanni XXIII Hospital, Bergamo, Italy
[7]Radboud university medical center, Nijmegen, The Netherlands
[8]Kent & Canterbury Hospital, Canterbury, UK
[9]Universita' Del Piemonte Orientale Ospedale Maggiore Della Carita', Novara, Italy
[10]Hospital del Mar-Parc de Salut Mar-IMIM, Barcelona, Spain
[11]University Medical Center Mannheim
[12]Ludwig-Maximilians University Munich, Department of Urology, Campus Grosshadern, Munich, Germany; Janssen Pharma Research and Development, Los Angeles, United States
[13]Medical University of Vienna, Vienna, Austria
[#]Current affiliation: Academic Urology Group, University of Cambridge, Addenbrooke's Hospital, Cambridge Biomedical Campus, Cambridge, UK
*Current affiliation: IRCCS Azienda Ospedaliera Universitaria San Martino, Genova, Italy

Corresponding Author:
Umberto Capitanio, MD
Unit of Urology, IRCCS San Raffaele Scientific Institute, Milan, Italy
Via Olgettina 60, 20132 Milan, Italy.
Tel. +39 02 26437286
E-mail: umbertocapitanio@gmail.com

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Abstract

Background: The role of lymph node dissection (LND) in renal cell carcinoma (RCC) is still under debate. We aimed to assess the utilization rates of LND over time in Europe.

Methods: A multi-institutional database of 13,581 RCC patients who underwent radical nephrectomy (RN) or nephron sparing surgery (NSS) between 1988 and 2014 was created within an European consortium. We analysed temporal trends in the frequency of LND by using Joinpoint regression. Logistic regression models were used to identify predictors of LND.

Results: Overall, 5,114 patients (42.7%) underwent LND. Lymph node invasion was recorded in 566 cases (11% of LND patients) which represents 4.7% of the whole study cohort. A gradual decline in the use of LND started in the 1990ies. After 2008 LND decreased significantly by 21.5% per year (95%CI -33.3 to -7.5, p<0.01) until 2011 and stabilized thereafter (Annual Percentage Change 4.9%, 95%CI -3.4 to 13.8, p=0.2). At multivariable analyses, patient age (OR 0.98, p<0.0001), type of surgery (RN vs. NSS: OR 5.46, p<0.0001), surgical approach (open vs. minimally invasive: OR 1.75, p<0.0001), T stage (T2 vs. T1: OR 1.57; T3-4 vs. T1: OR 1.44, p<0.0001), clinical tumour size (OR 1.14, p<0.0001), and year of surgery (OR 0.95, p<0.0001) were associated with higher probability of LND at nephrectomy.

Conclusions: A trend towards lower LND was observed over time for RCC patients who underwent RN or NSS. LND is more frequently performed in younger patients, locally advanced diseases and in case of open surgery.

Introduction

Surgery is the mainstay of therapy for patients with localised renal cell carcinoma (RCC) and an integral part of a multimodal therapeutic concept of patients presenting with metastatic disease [1-3]. The standard of surgical care, nephrectomy with lymphadenectomy, has been overshadowed by nephron-sparing surgery (NSS) in the past two decades. Data indicate that NSS is non-inferior to radical nephrectomy (RN) in terms of oncological outcomes[4], but may be associated with improved overall survival due to a decreased risk of cardiovascular events during follow-up[5].

Regional lymph node dissection (LND) is a well-accepted staging modality in RCC[6] and was traditionally performed from the bifurcation of the aorta to the crus of the diaphragm [7]. There are, however, limited data that support the therapeutic benefit of the use of this extended routine LND in clinical practice. Indeed, a randomized clinical trial demonstrated no survival benefit for performing a LND, but this trial included mainly patients with early stage disease [8]. Because of lack of high-quality data supporting its use and the unpredictable lymphatic drainage of RCC, no clear standards for indications and templates were established [9], and LND rates decreased dramatically. A publication from the United States showed that LND is currently performed in only 6.6% of nephrectomies [10]. This decrease has been reinforced by stage migration towards smaller tumours and the increasing adoption of minimally-invasive surgery [10]. The objective of the current study was to describe temporal trends and identify predictors of LND in a multicentre European cohort of patients with RCC.

Methods

Study population

For this retrospective study, all participating sites obtained institutional review board approval and provided the necessary institutional data sharing agreements before study initiation. The initial study cohort consisted of 13,581 consecutive patients with RCC who underwent RN or NSS from 1988 to 2014. No patient had preoperative systemic therapy. Cases with missing data were excluded (n=1,593, 11.7%), resulting in a cohort of 11,988 assessable patients.

Study variables

The collected variables were abstracted from patient charts and included age, gender, year of surgery, pathological TNM classification, clinical tumour size, treatment type (NSS vs. RN), surgical approach (open vs. laparoscopic vs. robotics), receipt of LND, LND template, and number of nodes removed. The database was frozen on 1-July-2016 and the final dataset was produced for current analyses.

Clinical and pathological TNM classifications were assigned according to the 2009 American Joint Committee on Cancer/Union Internationale Contre le Cancer definitions (AJCC/UICC) [1]. Cases before the introduction of the most recent classification scheme were reclassified. Clinical tumour size was based on preoperative imaging and defined as the greatest tumour diameter in centimetres. Pathological TNM and LND characteristics (number of positive or negative lymph nodes) were assessed at the single institution by dedicated expert uro-pathologist without a systematic central pathological review.

Outcome

The outcome of interest was receipt of a LND and the rate of lymph node invasion (LNI) during RN or NSS.

Statistical analyses

Frequencies and proportions were reported for categorical variables. Mean, medians and interquartile ranges (IQR) were calculated for continuously coded variables.

Temporal trends in the practice pattern of LND were evaluated using a piecewise regression approach that is implemented in the Joinpoint Regression Program (Version 4.1, National Cancer Institute, Bethesda, MD, United States). Joinpoint regression has been utilised to identify temporal trends in epidemiology, but has been successfully applied to evaluate trends in cancer diagnostics and therapies [11]. Specifically, the annual frequency of LND was modelled using a linear segmented regression function, with a log-transformed dependent variable, and inflection points corresponding to changes of slope. We allowed up to five inflection points, and the permutation test was used to identify the most parsimonious model. The presence of an inflection point was interpreted as a change in temporal trend of the use of LND and are reported as Annual Percentage Change (APC).

We used multivariable logistic regression to estimate the adjusted effects of each variable on the likelihood of receiving a LND. Covariates included age, year of surgery, country, pathological T stage, M stage, clinical tumour size, treatment type (NSS vs. RN), surgical approach [open vs. minimally invasive (laparoscopic or robotics)]. Adjusted odds ratios (OR), 95% confidence intervals (95% CI), and two-sided p-values were obtained. Similar analyses were repeated in the subgroup of patients (n=4,321, 36.0%) with available information regarding the LND template (anatomical region of LND and number of lymph nodes removed).

Statistical analyses were performed using SPSS version 20 (IBM Corp., Somers, NY, United States) and the Joinpoint Regression Program (National Cancer Institute, Bethesda, MD, United States). All tests were two-sided with a significance level set at $p<0.05$.

Results

Table 1 shows the descriptive characteristics of the patients included. Overall, 5,114 of 11,988 patients (42.7%) underwent LND. PN patients underwent LND less frequently relative to RN counterparts (PN 28.8% vs RN 50.1%, p<0.001). Among patients treated with LND, pathological LNI was recorded in 566 cases (11.0%), representing 4.7% of the entire study cohort.

Temporal trends in LND

A gradual decline in the use of LND started in the 1990ies and dramatically occurred in 2008 (Figure 1A). Specifically, the proportion of patients who underwent LND showed an initial but insignificant increase between 1988 and 1990 (APC 10.1%, 95% CI -6.6 to 29.7, p=0.2), followed by a significant decline by 3.6% per year until 2002 (95% CI -4.7 to -2.5, p<0.01). Following an increase by 6.0% between 2002 and 2008 (95% CI 2.2 to 10.0, p<0.01), after 2008 LND decreased significantly by 21.5% per year (95% CI -33.3 to -7.5, p<0.01) until 2011 and stabilized thereafter (APC 4.9%, 95% CI -3.4 to 13.8, p=0.2).

Changes observed in patients with pT1 disease mirrored findings from the overall cohort and recently stabilized at around 10% (Figure 2A). LND in pT2 disease declined between 1988 and 1995 (APC -5.2%, 95% CI -9.8 to -0.3, p<0.01), which was followed by non-significant changes between 1995 and 2008 (APC 1.5%, 95% CI -0.7 to 3.8, p=0.2). From 2008 to 2014, there was a significant decline (APC -12.4%, 95% CI -17.8 to 6.6, p<0.01) (Figure 2B). There were no significant changes in the LND rate among patients with pT3-4 disease (APC 0.1%, p=0.7) (Figure 2C). The LND rate in M0 disease decreased initially by 1.9% per year (95% CI -2.9 to -0.9, p<0.01), followed by non-significant changes between 2004 and 2008. From 2008 to 2011, the LND rate dropped by 28.9% per year (95% CI -45.5 to -7.1, p<0.01) and stabilized thereafter (p=0.4) (Figure 2D). No changes in the LND rate were seen in M1 disease (APC -0.3%, p=0.4) (Figure 2E).

As regards type of surgery and approach, during open surgery, there was a significant decline in LND between 1988 and 2005 by 2.9% per year (95% CI -3.5 to -2.2, p<0.01). Between 2005 and 2008, there was a marginally significant trend towards a rising proportion of LND (APC 21.5%, 95% CI -0.1 to 47.8, p=0.07), followed by a significant decrease (APC -21.0%, 95% CI -35.0 to -0.8, p=0.03) and a recent increase (APC 10.3%; p=0.05) (Figure 3A). The LND rate during laparoscopic surgery continuously declined, except between 2005 and 2008 (Figure 3B). During the early years of adoption, LND was rarely used during robotic surgery. A recent increase was seen, but this was not statistically significant (p=0.1) (Figure 3C). Among patients who underwent NSS a significant decline was observed after 2012 (APC -99.5%, p=0.02) (Figure 3D). During RN, there was an initial increase in LND (APC 18.9%, 95% CI 9.3 to 29.4, p<0.01), followed by non-significant changes until 1999 (p=0.1 and p=0.5, respectively). After a significant increase between 1999 and 2007 (APC 7.4%, 95% 5.0 to 9.9, p<0.01), LND decreased until 2011 (APC -11.6%, 95% CI -18.7 to -3.8, p<0.01). There was recent significant increase between 2011 and 2014 (Figure 3E).

There was a statistically significant increase of surgeries in which no LND was performed (p<0.05 for 1988-1998 and 1998-2014, respectively) (Figure 4A). The rates of hilar LND declined continuously (APC -3.8%, 95% CI -5.1 to -2.5, p<0.01), similarly to side-specific LND (APC -3.6%, 95% CI -4.6 to -2.6, p<0.01) (Figure 4B-C). The extended LND rate decreased significantly until 2001 (APC -14.7%, 95% CI -18.1 to 11.2, p<0.01), and stabilized thereafter at a rate of around 6% (p=0.8) (Figure 4D).

After 2008, less than 8% of the patients received an extended LND at the time of nephrectomy.

Predictors of LND

On multivariable analyses, patient age (OR 0.98, 95% CI 0.97-0.99, p<0.0001), type of surgery (RN vs. NSS: OR 5.46, 95%CI 5.00-6.63, p<0.0001), surgical approach (open vs. minimally invasive: OR 1.75, 95%CI 1.43-2.13, p<0.0001), T stage (T2 vs. T1: OR 1.57 95%CI 1.19-2.07; T3-4 vs. T1: OR 1.44 95%CI 1.20-1.73, p<0.0001), clinical size (OR 1.14, 95%CI 1.11-1.14, p<0.0001) and year of surgery (OR 0.95, 95%CI 0.94-0.96, p<0.0001) were independent predictors of LND.

Temporal trends in LNI

Although the percentage of LNI remained stable over time in case of locally-advanced disease (LNI rate: 12% in 1988-1996 vs. 12% in 2008-2014, Figure 5), it declined in patients with pT1 (LNI rate: 6.2% in 1988-1996 vs. 3.9% in 2008-2014, Figure 5) or pT2 disease (LNI rate: 1.7% in 1988-1996 vs. 0.4% in 2008-2014, Figure 5). On multivariable analyses adjusted for the effects of patient and tumour characteristics, year of surgery was not associated with the probability of LNI (p=0.3).

Discussion

Although the majority of RCC patients are diagnosed with small organ-confined disease, up to 40% of patients harbour locally advanced disease or distant metastases [3]. In these specific scenarios, LNI confirmation has paramount implications for risk stratification and prognosis. Indeed, LNI remains one of the most informative predictors of the natural history of the disease, even in the setting of metastatic RCC [12,13]. Follow-up strategies require precise risk estimation [14] and the lack of a correct nodal status assessment may underestimate the actual disease burden with critical consequences for any adjuvant [15] or salvage [6] strategy.

Although some previous reports suggested a potential role in terms of survival benefit for LND [6,9], the conclusion of the one and only randomized clinical trial [8] together with the findings of other retrospective studies seem to deny any potential effect in terms of cancer control [16-18]. More specifically, Gershman et al. evaluated the association of LND with oncologic outcomes among patients undergoing radical nephrectomy (RN) for both non-metastatic [16] and metastatic RCC [17]. They provided evidence that LND was associated with improved oncologic outcomes even among patients at increased risk of pN1 disease, including those with preoperative radiographic lymphadenopathy, and after stratification for increasing threshold probabilities of pN1 disease ranging from 0.05 to 0.50 [16].

Due to the above cited controversies, there are currently no formal guidelines regarding the extent or nodal template of LND at the time of radical nephrectomy and the use of LND by urologists was never formally assessed outside the United States. In such specific geographic setting, Kates and colleagues analysed changes over time in LND use. In their report, only 6.6% of the patients received LND [10]. There was a gradual decline in LND beginning in 1988 that accelerated after 1997, with the period

1998–2005 having significantly decreased odds of LND relative to the period 1988–1997[10]. According to the authors, such a decline was driven by (1) the diffusion of laparoscopic nephrectomy throughout the US in the late 1990s; (2) the increased use of cross-sectional imaging in the 1990s led to tumours being identified at a more localized stage and at a smaller size; (3) an evidenced-based transition because publications in the late 1990s minimized the importance of LND; (4) the lack of a discrete common procedural terminology billing code for LND during radical nephrectomy [10].

To the best of our knowledge no data assessed the same topic in a European setting. Therefore, the current study should be regarded as the first formal assessment of the temporal trends of LND use in RCC and of the relative impact of stage migration and the introduction of minimally invasive technique on LND utilization rates. Our data show key aspects regarding LND utilization. First, there was a trend towards lower use of LND starting in the 1990ies (Figure 1A). A sharp decrease was observed in 2008 (Figure 1A) after the publication of the EORTC trial showing no benefit in terms of survival. This observation should be regarded as a unique example of the effect of level 1 evidence on the European Urological community. It is also of note that the European urologists have applied the EORTC data to organ-confined disease only, maintaining an elevated percentage of LND in high-risk patients. A little more worrisome is the drop registered in case of pT2 tumours (LND range 55.8-82.1% before 2008 vs. 25-54.2% after 2008) considering that the prevalence of LNI among patients with larger tumours in not negligible [12]. Correspondingly, the percentage of LNI among T2 cases dropped from 6.8% to 3.9% after the decrease in LND utilization registered after 2008.

Second, the current study does report key information about the trend over time of LND utilization rates according to the type of surgery (NSS vs. RN) and surgical approach (open vs. laparoscopy vs. robotic), that were lacking in the the report by Kates and colleagues[10]. The decline in the use of LND was more pronounced among cases treated with NSS relative to RN (LND range 12.2-33.3% before 2008 vs. 1.8-6.5% after 2008) and among cases treated with laparoscopy relative to open surgery (LND range 14.7-95.2% before 2008 vs. 14.2-25.7% after 2008). Such important findings were also confirmed after accounting for different confounders. On the other hand, due to the intrinsic technical difficulties in performing a retroperitoneal LND laparoscopically, our findings depict also the potential role of robotic surgery, even in case of RN, if LND is planned.

Third, besides the declining rate, LND is usually anatomically limited, with only 4.5-8.2% of the patients receiving an extended LND at the time of renal surgery. This feature is consistent with previous findings suggesting that the majority of LND are restricted to the hilar area without any drive in terms of further extension[10,19].

Although the current study represents the first formal assessment of the temporal trends and the determinants of the use of LND in Europe, is not devoid of limitations. Since no European population-based database exists to address the topic also in community hospitals, the current findings are applicable to tertiary care or academic centres only. Missing information in terms of comorbidities, surgical expertise and learning curve and disparities among the centers as regards diagnostic and therapeutic standards might somehow affect the results. Moreover, due to the multi-institutional nature of the database, it is possible that the protocol for pathological assessment might be different across all the different center and during the entire study period.

Conclusions

A trend towards lower LND was observed over time for RCC patients who underwent RN or NSS. LND is more frequently performed in younger patients, locally advanced diseases and in case of open surgery.

Conflict of interest

None

Acknowledgements

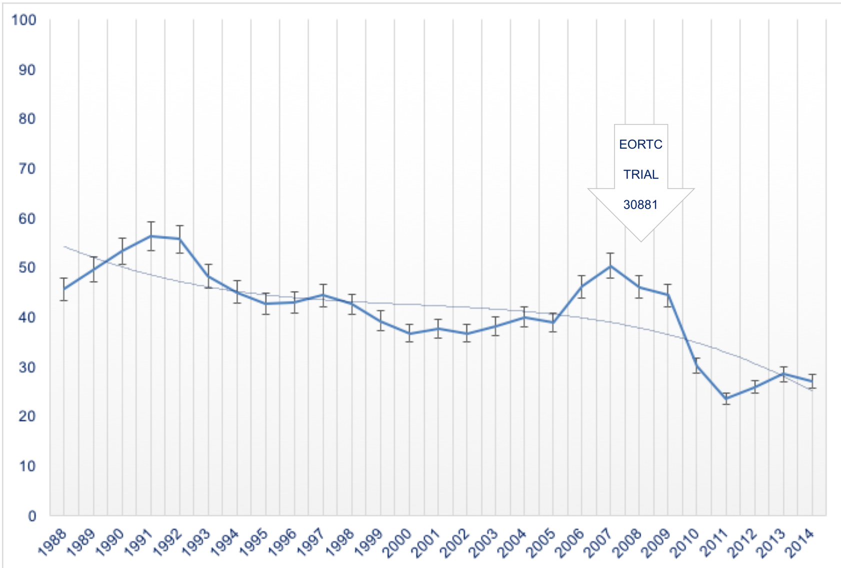
None

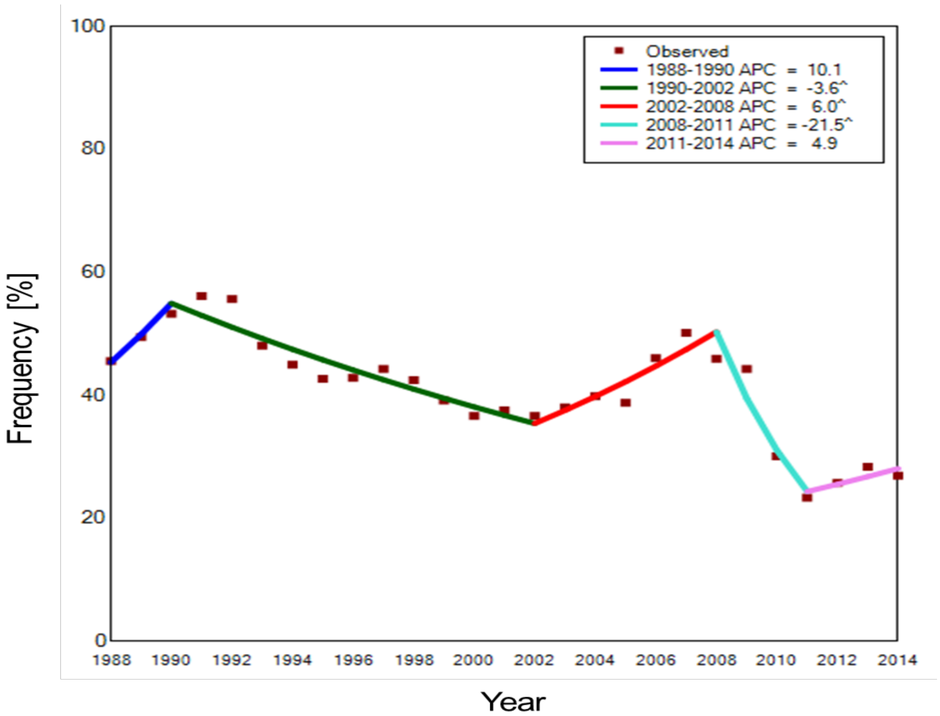
Table 1: Descriptive characteristics of the overall cohort (n=11,988, 100%).

Variable	
Age* (years)	62 (60.9) 53-70
Clinical size* (cm)	5 (5.8) 3-8
cN	
0	75.3%
1	8.8%
Missing	15.9%
M stage (#)	
M0	90.3%
M1	9.7%
pT stage (#)	
T1	57.6%
T2	9.9%
T3-4	32.4%
pN	
x	53.2%
0	42.1%
1	4.7%
Year of surgery*	2002 (2001) 2002-2007
Treatment type (#)	
RN	70.9%
NSS	29.1%
Surgical approach (#)	
open	79.9%
laparoscopic	19.1%
robotic	1.0%

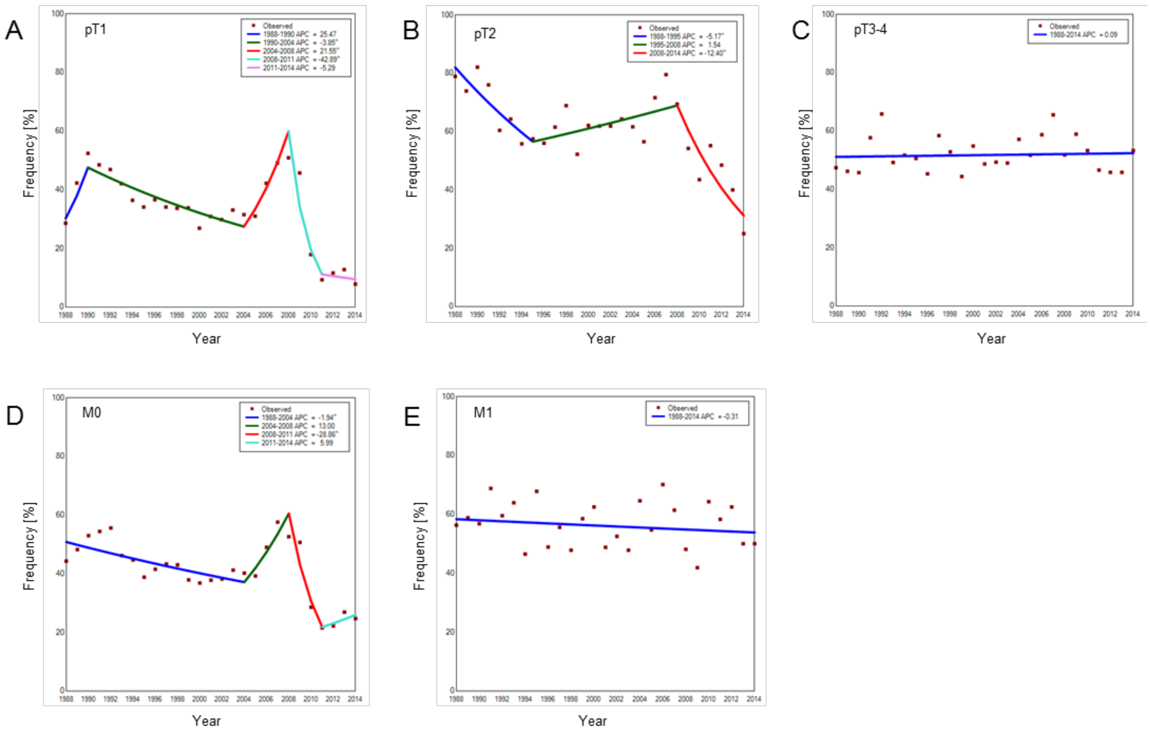
**Median (Mean), InterQuartile Range (IQR)*
#Percentage

Figures 1A-B: Temporal trend in the use of LND in 11,988 patients undergoing RN or NSS. 1A) 95% Confidence Intervals and polynomial trendline are reported. 1B) The data markers plot the annual frequencies, and coloured lines demonstrate the results of the Joinpoint regression analysis. ^APC was significantly different from zero at alpha=0.05.

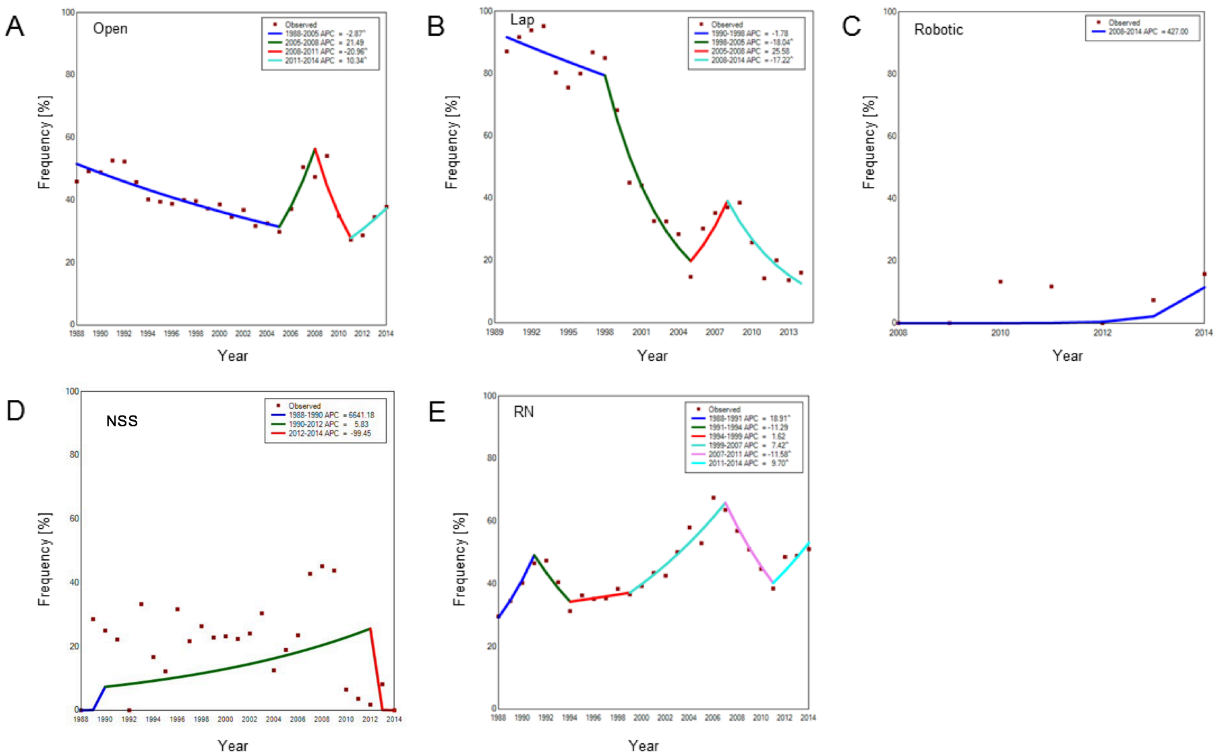




Figures 2A-B-C-D-E: Temporal trends in utilisation of LND in 11,988 patients according to T stage (A=pT1, B=pT2, C=pT3-4) and M stage (D=M0, E=M1). ^APC was significantly different from zero at alpha=0.05.



Figures 3A-B-C-D-E: Temporal trends in utilisation of LND in 11,988 patients according to procedure type (A=open surgery, B=laparoscopic surgery, C=robotic surgery, D=nephron-sparing surgery, E=radical nephrectomy). ^APC was significantly different from zero at alpha=0.05.



Figures 4A-B-C-D: Temporal trends in the utilization of LND in 4,321 patients according to the site of LND (A=no LND, B=hilar LND, C=side-specific LND, D=extended LND). ^APC was significantly different from zero at alpha=0.05.

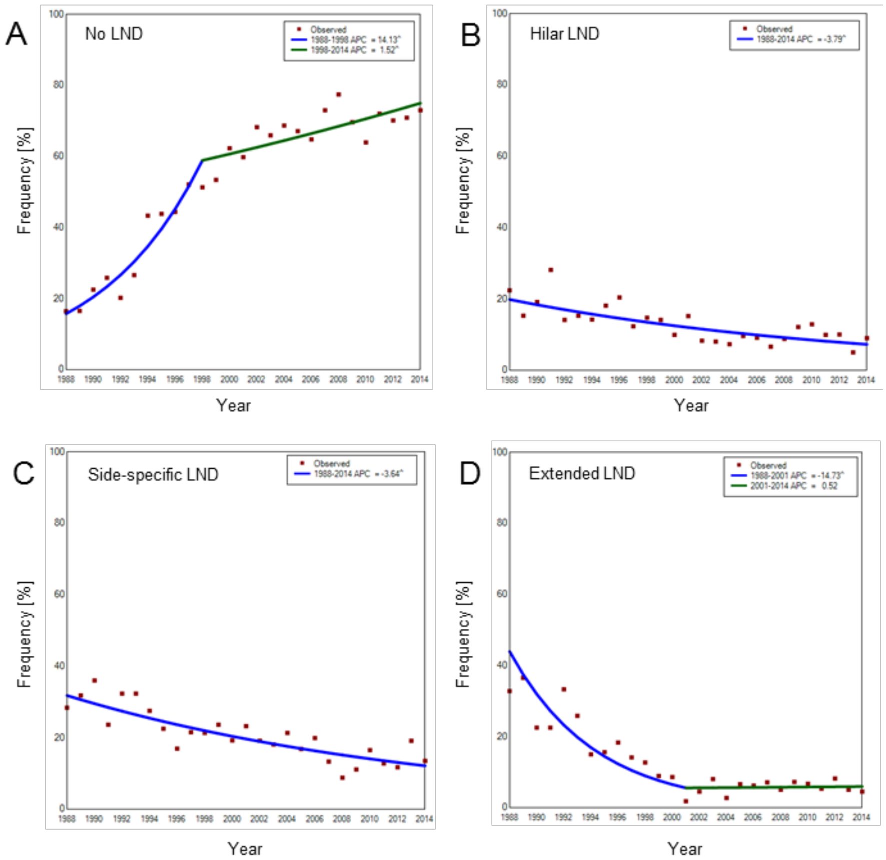
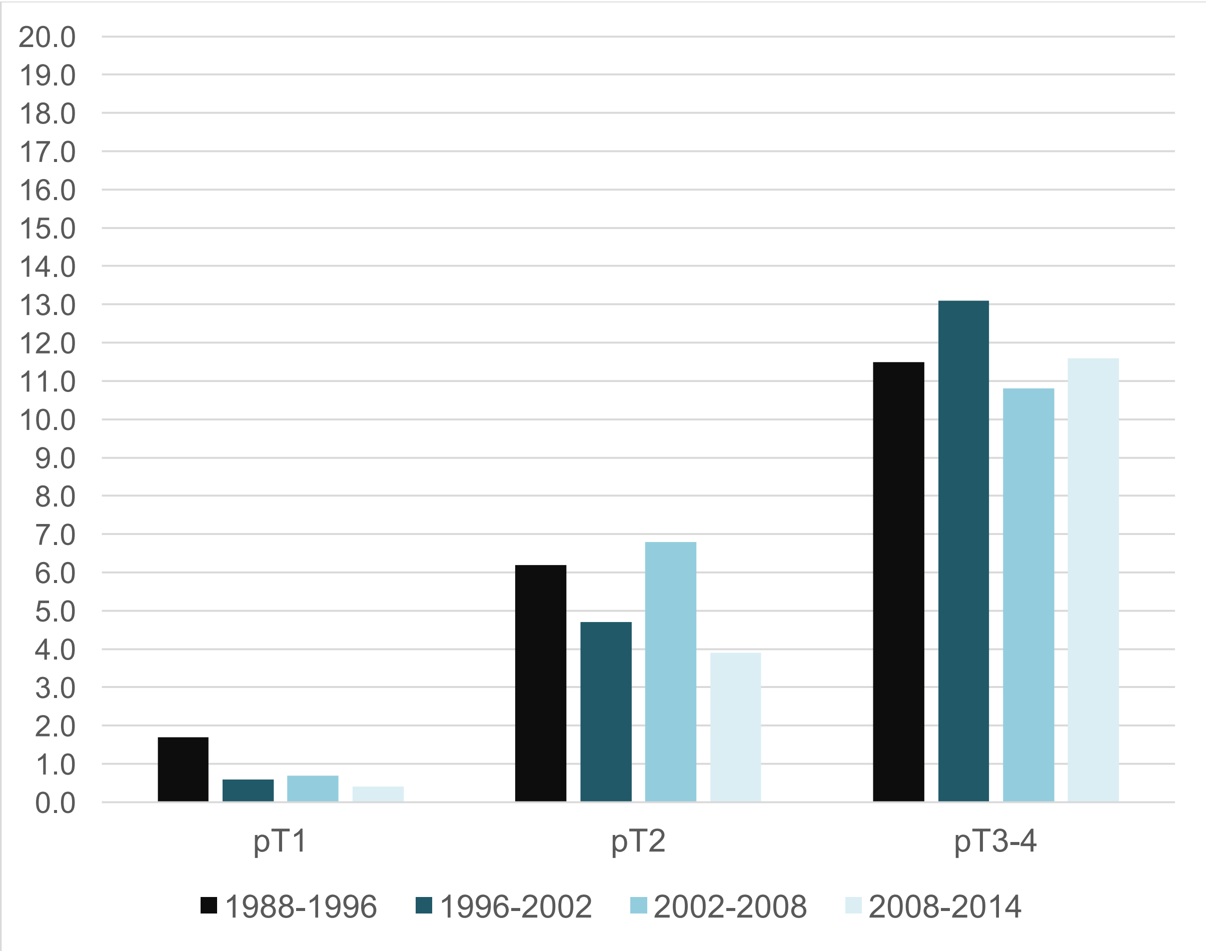


Figure 5: Percentage of patients with pathological confirmation of lymph node invasion (LNI, %) stratified for year of surgery and T stage.



References

[1] Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU Guidelines on Renal Cell Carcinoma: 2014 Update. Eur Urol 2015;67:913–24. doi:10.1016/j.eururo.2015.01.005.

[2] NCCN Guidelines - Kidney Cancer Version 3.2015 2015:1–50.

[3] capitanio U, Montorsi F. Renal cancer. The Lancet 2016;387:894–906. doi:10.1016/S0140-6736(15)00046-X.

[4] Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2011;59:543–52. doi:10.1016/j.eururo.2010.12.013.

[5] capitanio U, Terrone C, Antonelli A, Minervini A, Volpe A, Furlan M, et al. Nephron-sparing techniques independently decrease the risk of cardiovascular events relative to radical nephrectomy in patients with a T1a-T1b renal mass and normal preoperative renal function. Eur Urol 2015;67:683–9. doi:10.1016/j.eururo.2014.09.027.

[6] Moschini M, Dell'Oglio P, Larcher A, capitanio U. Lymph node dissection for renal cell carcinoma: what are we missing? Current Opinion in Urology 2016. doi:10.1097/MOU.0000000000000312.

[7] ROBSON CJ. Radical nephrectomy for renal cell carcinoma. Journal of Urology 1963;89:37–42.

[8] Blom JHM, Van Poppel H, Maréchal JM, Jacqmin D, Schröder FH, de Prijck L, et al. Radical Nephrectomy with and without Lymph-Node Dissection: Final Results of European Organization for Research and Treatment of Cancer (EORTC) Randomized Phase 3 Trial 30881 2009;55:28–34. doi:10.1016/j.eururo.2008.09.052.

[9] capitanio U, Becker F, Blute ML, Mulders P, Patard J-J, Russo P, et al. Lymph node dissection in renal cell carcinoma. Eur Urol 2011;60:1212–20. doi:10.1016/j.eururo.2011.09.003.

[10] Kates M, Lavery HJ, Brajtbord J, Samadi D, Palese MA. Decreasing Rates of Lymph Node Dissection During Radical Nephrectomy for Renal Cell Carcinoma 2012;19:2693–9. doi:10.1245/s10434-012-2330-6.

[11] Melamed A, Hinchcliff EM, Clemmer JT, Bregar AJ, Uppal S, Bostock I, et al. Trends in the use of neoadjuvant chemotherapy for advanced ovarian cancer in the United States. Gynecologic Oncology 2016;143:236–40. doi:10.1016/j.ygyno.2016.09.002.

[12] capitanio U, Jeldres C, Patard J-J, Perrotte P, Zini L, la Taille de A, et al. Stage-specific effect of nodal metastases on survival in patients with non-metastatic renal cell carcinoma 2009;103:33–7. doi:10.1111/j.1464-410X.2008.08014.x.

[13] Lughezzani G, capitanio U, Jeldres C, Isbarn H, Shariat SF, Arjane P, et al. Prognostic significance of lymph node invasion in patients with metastatic renal cell carcinoma. Cancer 2009;115:5680–7. doi:10.1002/cncr.24682.

[14] Lobo JM, Nelson M, Nandanan N, Krupski TL. Comparison of Renal Cell Carcinoma Surveillance Guidelines: Competing Trade-Offs. Journal of Urology 2016:1–7. doi:10.1016/j.juro.2015.12.094.

[15] Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al.

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med 2016:NEJMoa1611406–9. doi:10.1056/NEJMoa1611406.
[16] Gershman B, Thompson RH, Moreira DM, Boorjian SA, Tollefson MK, Lohse CM, et al. Radical Nephrectomy With or Without Lymph Node Dissection for Nonmetastatic Renal Cell Carcinoma: A Propensity Score-based Analysis. Eur Urol 2016. doi:10.1016/j.eururo.2016.09.019.
[17] Gershman B, Thompson RH, Moreira DM, Boorjian SA, Lohse CM, Costello BA, et al. Lymph Node Dissection is Not Associated with Improved Survival among Patients Undergoing Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma: A Propensity Score Based Analysis. J Urol 2016. doi:10.1016/j.juro.2016.09.074.
[18] Sun M, Trinh Q-D, Bianchi M, Hansen J, Abdollah F, Tian Z, et al. Extent of lymphadenectomy does not improve the survival of patients with renal cell carcinoma and nodal metastases: biases associated with the handling of missing data. BJU Int 2013;113:36–42. doi:10.1111/j.1464-410X.2012.11693.x.
[19] Hutterer GC, Patard J-J, Perrotte P, Ionescu C, la Taille de A, Salomon L, et al. Patients with renal cell carcinoma nodal metastases can be accurately identified: External validation of a new nomogram. Int J Cancer 2007;121:2556–61. doi:10.1002/ijc.23010.