Pieter DeMulder lecture

Irresistible Rise of Minimally Invasive Treatments in Localized RCC

Peter Mulders, MD, PhD
Department of Urology
Radboud University Medical Centre
Nijmegen, The Netherlands
RCC is the Most Common Renal Cancer but an orphan disease

- 80-85% of renal cancers\(^1\)
- 2-3% of adult malignancies\(^2\)
- 63,000 new cases/year in Europe
- 26,000 mortalities annually
- More common in men\(^3\)
- Frequent in elderly\(^4\)
- More common in North Europe and America\(^3,4\)

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Rise of incidence

Absolute incidence of renal cancer in the Netherlands

Year of diagnosis

Number of renal cancer

Males
Females
Stage migration

**Absolute incidence of renal cancer by disease stage in the Netherlands**

*Stage I size decrease from 4.1 to 3.2 cm*
A Changing Paradigm

- Robson open tumor nephrectomy
  - Vessels first
  - Radical nephrectomy
  - Lymph node dissection

To

- Robotic assisted laparoscopic partial nephrectomy
  - Laparoscopy - Robot
  - Nephron sparing
Yes, in centres of expertise they are in terms of:

- Oncological safety
- Complication rate
- Ischemia time

PN

RN
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

Hendrik Van Poppel\textsuperscript{a,*}, Luigi Da Pozzo\textsuperscript{b,1}, Walter Albrecht\textsuperscript{c}, Vsevolod Matveev\textsuperscript{d}, Aldo Bono\textsuperscript{e}, Andrzej Borkowski\textsuperscript{f}, Marc Colombel\textsuperscript{g}, Laurence Klotz\textsuperscript{h}, Eila Skinner\textsuperscript{i}, Thomas Keane\textsuperscript{j}, Sandrine Marreaud\textsuperscript{k}, Sandra Collette\textsuperscript{k}, Richard Sylvester\textsuperscript{k}

First Level I evidence

Partial and radical nephrectomy deliver comparable oncological safety

*Tumor size : up to 5 cm*
Partial Versus Radical Nephrectomy for 4 to 7 cm Renal Cortical Tumors

R. Houston Thompson, Sameer Siddiqui, Christine M. Lohse, Bradley C. Leibovich, Paul Russo and Michael L. Blute*

From the Departments of Urology (RHT, SS, BCL, MLB) and Health Sciences Research (CML), Mayo Medical School and Mayo Clinic, Rochester, Minnesota, and Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center (RHT, PR), New York, New York

![Graph showing cancer-specific survival over years from surgery to last follow-up with PN not inferior and Tumor size 4 - 7 cm, Total 1150 pat., PN 286 pat., RN 873 pat.](image-url)
### Table: Meta analysis; RCC Guidelines

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**Conclusions:** The evidence base suggests localised RCCs are best managed by nephron-sparing surgery where technically feasible. However, the current evidence base has significant limitations due to studies of low methodological quality marked by high risks of bias.
LOSS OF RENAL FUNCTION (=MASS) IS A MAJOR RISK FACTOR!

<table>
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<th>eGFR (ml/min)</th>
<th>45-60</th>
<th>30&lt;45</th>
<th>15&lt;30</th>
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<td>1.2</td>
<td>1.8</td>
<td>3.2</td>
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<td>1.4</td>
<td>2.0</td>
<td>2.8</td>
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<td>HOSPITALIZATION</td>
<td>1.1</td>
<td>1.5</td>
<td>2.1</td>
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1,120,295 PATIENTS, m FU 2.3yrs

PARTIAL NEPHRECTOMY AVOIDS SIGNIFICANT RENAL FUNCTION LOSS

HUANG: LANCET ONCOL, 7:735, 2006
Every Minute Counts When the Renal Hilum Is Clamped During Partial Nephrectomy

R. Houston Thompsona,*,1, Brian R. Laneb,1, Christine M. Lohsea, Bradley C. Leibovicha, Amr Ferganyc, Igor Franka, Inderbir S. Gillc, Michael L. Blutea, Steven C. Campbella

a Mayo Medical School and Mayo Clinic, Rochester, MN, USA
b Glickman Urological Institute; Cleveland Clinic Foundation, Cleveland, OH, USA
c Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

(17%) developed new-onset stage IV chronic kidney disease during follow-up. As a continuous variable, longer warm ischemia time was associated with ARF (odds ratio: 1.05 for each 1-min increase; p < 0.001) and a GFR < 15 (odds ratio: 1.06; p < 0.001) in the postoperative period, and it was associated with new-onset stage IV chronic kidney disease (hazard ratio: 1.06; p < 0.001) during follow-up. Similar results were

Conclusions: Longer warm ischemia time is associated with short- and long-term renal consequences. These results suggest that every minute counts when the renal hilum is clamped.
PROTECTION AGAINST ISCHEMIC DAMAGE

• HYDRATION OF PATIENTS (> 3ml U/min)

• 3ml/kg 15% MANNITOL PRIOR TO AND AFTER CLAMPING OF ARTERY

• OCCLUSION OF RENAL ARTERY ONLY, WITH EXTENSIVE DISSECTION TOPICAL PAPAVERINE (1mg/kg)

• IF ISCHEMIA > 20 MINUTES ANTICIPATED RENAL HYPOTHERMIA
Renal Function After Nephron-sparing Surgery Versus Radical Nephrectomy: Results from EORTC Randomized Trial 30904

Emil Scosyrev\textsuperscript{a}, Edward M. Messing\textsuperscript{a,*}, Richard Sylvester\textsuperscript{b}, Steven Campbell\textsuperscript{c}, Hendrik Van Poppel\textsuperscript{d}

Fig. 2 - Mean estimated glomerular filtration rate as a function of time by assigned treatment (vertical bars indicate point-wise 95% confidence intervals). eGFR = estimated glomerular filtration rate; NSS = nephron-sparing surgery; RN = radical nephrectomy.
Yes, in centres of expertise they are in terms of:

- Oncological safety
- Complication rate
- Ischemia time

Open PN

Lap PN
Comparison of 1,800 Laparoscopic and Open Partial Nephrectomies for Single Renal Tumors

Inderbir S. Gill, Louis R. Kavoussi, Brian R. Lane, Michael L. Blute, Denise Babineau, J. Roberto Colombo, Jr., Igor Frank, Sompol Permpongkosol, Christopher J. Weight, Jihad H. Kaouk, Michael W. Kattan and Andrew C. Novick*

cant). When comparing 514 LPNs and 676 OPNs, the Kaplan-Meier estimate of 3-year cancer specific survival was 99.3% (95% CI 98.0, 100) and 99.2% (95% CI 98.4, 100), respectively. At 3 years Kaplan-Meier estimates of local recurrence rates were 1.4% (95% CI 0, 2.8) and 1.5% (95% CI 0.4, 2.6), and the distant recurrence rates were 0.9% (95% CI 0, 2.2) and 2.1% (95% CI 0.7, 3.4) in the LPN and OPN groups, respectively.
7-Year Oncological Outcomes After Laparoscopic and Partial Nephrectomy

Brian R. Lane*, † and Inderbir S. Gill‡, §

\( n = 387 \) [ LPN : 77 pat. / OPN : 310 pat. ]

Cancer - specific survival

Metastasis - free survival
800 Laparoscopic Partial Nephrectomies: A Single Surgeon Series

Inderbir S. Gill,* † Kazumi Kamoi, Monish Aron and Mihir M. Desai‡

From the USC Institute of Urology, Keck School of Medicine, University of Southern California, Los Angeles, California and Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio

<table>
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<th>Overall complications</th>
<th>No. Era 1</th>
<th>No. Era 2 (%)</th>
<th>No. Era 3 (%)</th>
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<td>Intraop:</td>
<td>66 (23.9)</td>
<td>43 (14.9)</td>
<td>25 (10.6)</td>
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<td>Visceral injury</td>
<td>9 (3.3)</td>
<td>9 (3.1)</td>
<td>6 (2.6)</td>
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<td>Open conversion</td>
<td>5 (1.8)</td>
<td>4 (1.4)</td>
<td>2 (0.9)</td>
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<tr>
<td>Conversion to LRN‡</td>
<td>2 (0.7)</td>
<td>3 (1.0)</td>
<td>0</td>
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<td>Postop:</td>
<td>61 (22.1)</td>
<td>36 (12.5)</td>
<td>20 (8.5)</td>
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<td>Hemorrhage</td>
<td>18 (6.5)</td>
<td>10 (3.5)</td>
<td>5 (2.1)</td>
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<tr>
<td>Urine leakage</td>
<td>10 (3.6)</td>
<td>5 (1.7)</td>
<td>4 (1.7)</td>
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<tr>
<td>Conversion to LRN§</td>
<td>2 (0.7)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
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<tr>
<td>Urological complications</td>
<td>26 (9.4)</td>
<td>14 (4.8)</td>
<td>9 (3.8)</td>
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J Urol 183: 34 - 42, 2010
Guidelines

**EAU Guidelines on Renal Cell Carcinoma: The 2010 Update**

Börje Ljungberg\(^a\), Nigel C. Cowan\(^b\), Damian C. Hanbury\(^c\), Milan Hora\(^d\), Markus A. Kuczyk\(^e\), Axel S. Merseburger\(^e\), Jean-Jacques Patard\(^f\), Peter F.A. Mulders\(^g\), Ioanel C. Sinescu\(^h\)

- Partial nephrectomy should be performed in pT1a (and pTb)
- Laparoscopy should be done in experienced hands
And what’s about the robot?

Are there comparative trials versus conventional laparoscopic partial nephrectomy?
Robotic and laparoscopic partial nephrectomy: a matched-pair comparison from a high-volume centre

Monish Aron, Phillipe Koenig, Jihad H. Kaouk, Mike M. Nguyen, Mihir M. Desai and Inderbir S. Gill

RESULTS

Between July 2006 and August 2007, 12 selected patients had RPN for a single small unilateral renal mass. The perioperative and 3-month functional outcomes were compared with those of 12 matched patients treated with LPN in the

Overall there were no differences in perioperative variables (WIT, estimated blood loss, surgery time, length of stay) between the groups. Fewer ports were used during LPN. Renal functional outcomes, transfusion rate and complication rates were comparable. Two RPN cases required conversion to standard LPN. A subset
Robotic Versus Laparoscopic Partial Nephrectomy: Single-surgeon Matched Cohort Study of 150 Patients

Georges-Pascal Haber, Wesley M. White, Sebastien Crouzet, Michael A. White, Sylvain Forest, Riccardo Autorino, and Jihad H. Kaouk

Laparoscopic PN : 186 pat. / RAPN : 75 pat.

for LPN ($P = .75$). Mean estimated blood loss (EBL) was higher in the RPN cohort (323 vs 222 mL, $P = .01$). There was no significant difference with respect to warm ischemia time (18.2 minutes vs 20.3 minutes, $P = .27$), length of hospitalization ($P = .84$), percent change in eGFR ($P = .80$), or adverse events ($P = .52$). All surgical margins were negative.

RPN offers at least comparable outcomes
Robotic Partial Nephrectomy Versus Laparoscopic Partial Nephrectomy for Renal Cell Carcinoma: Single-Surgeon Analysis of >100 Consecutive Procedures

Agnes J. Wang and Sam B. Bhayani
From the Division of Urology, Washington University School of Medicine, St. Louis, Missouri

No statistically significant differences were found between the groups with regard to age, body mass index, or American Society of Anesthesiologists score. No significant difference was found between the estimated blood loss (136 vs 173 mL), tumor size (2.5 vs 2.4 cm), need for pelvicaliceal repair (56% for both), and positive margin rate (1 vs 1 patient) between RPN and LPN, respectively. The mean total number of trocars in the robotic group was greater than the laparoscopic group (4.6 vs 3.2, \( P = .01 \)). The mean total operative time (140 vs 156 minutes, \( P = .04 \)), warm ischemia time (19 vs 25 minutes, \( P = .03 \)), and length of stay (2.5 vs 2.9 days, \( P = .03 \)) were significantly shorter for RPN than for LPN, respectively.

Brian M. Benway,* Sam B. Bhayani,† Craig G. Rogers,† Lori M. Dulabon, Manish N. Patel, Michael Lipkin, Agnes J. Wang and Michael D. Stifelman†

From the Division of Urologic Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri (BMB, SBB, AJW), Vattikuti Urology Institute, Henry Ford Hospital, Detroit, Michigan (CGR, MNP), and Division of Urologic Oncology, Department of Urology, NYU Langone Medical Center, New York, New York (LMD, ML, MDS)

complexity did affect these factors for laparoscopic partial nephrectomy. In addition, for simple and complex tumors robot assisted partial nephrectomy provided significantly shorter warm ischemic time than laparoscopic partial nephrectomy (15.3 vs 25.2 minutes for simple, p < 0.0001; 25.9 vs 36.7 minutes for complex, p = 0.0002). There were no intraoperative complications during robot

Warm ischemia times were significantly shorter in the robot assisted partial nephrectomy series (19.7 vs 28.4 minutes, p < 0.0001).
Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) Classification of Renal Tumours in Patients who are Candidates for Nephron-Sparing Surgery

Vincenzo Ficarra\textsuperscript{a,}\textsuperscript{*}, Giacomo Novara\textsuperscript{a}, Silvia Secco\textsuperscript{a}, Veronica Macchi\textsuperscript{b}, Andrea Porzianato\textsuperscript{b}, Raffaele De Caro\textsuperscript{b}, Walter Artibani\textsuperscript{a}
### PADUA complexity scoring system

#### Anatomical features

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<th>Score</th>
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<td>Longitudinal (polar) location</td>
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<td>Superior/inferior</td>
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<td>Middle</td>
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<tr>
<td>≥50%</td>
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<td>&lt;50%</td>
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<td>Urinary collecting system</td>
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<td>≤4</td>
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<td>4.1–7</td>
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<tr>
<td>&gt;7</td>
<td>3</td>
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* Anterior or posterior face can be indicated with a letter (“a” or “p”) following the score.
• RESULTS

• Overall complications: 37 case (22.6%)
• Bleeding 21 case/ 1 spleen injury/ 1 pleural injury
• Most severe complication: Clavien 3b (spleen/ pleural injury)
• Complications: correlated with polar location of the tumor/ rim-location of the tumor/ involvement of sinus/ percentage of tumor deepening in the kidney.
• No correlation with tumor size (!)

PADUA score:
• between 8-9 14x higher risk of complications than below 7
• > 10: 30x higher risk of complication
The R.E.N.A.L. Nephrometry Score: A Comprehensive Standardized System for Quantitating Renal Tumor Size, Location and Depth

Alexander Kutikov and Robert G. Uzzo*

*From the Department of Urological Oncology, Fox Chase Cancer Center, Temple University School of Medicine, Philadelphia, Pennsylvania

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<td><strong>R</strong>adius (maximal diameter in cm)</td>
<td>(\leq 4)</td>
<td>&gt;4 but &lt; 7</td>
<td>(\geq 7)</td>
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<tr>
<td><strong>E</strong>xophytic/endophytic properties</td>
<td>(\geq 50%)</td>
<td>&lt;50%</td>
<td>Entirely endophytic</td>
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<td><strong>N</strong>earness of the tumor to the collecting system or sinus (mm)</td>
<td>(\geq 7)</td>
<td>&gt;4 but &lt; 7</td>
<td>(\leq 4)</td>
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<tr>
<td><strong>L</strong>ocation relative to the polar lines*</td>
<td>Entirely above the upper or below the lower polar line</td>
<td>Lesion crosses polar line</td>
<td>&gt;50% of mass is across polar line (a) or mass crosses the axial renal midline (b) or mass is entirely between the polar lines (c)</td>
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* suffix “h” assigned if the tumor touches the main renal artery or vein
R.E.N.A.L score

• CONCLUSIONS

• R.E.N.A.L. Score enables comparison and standardized communication regarding the anatomical features of solid renal masses.

• Especially useful for literature comparison

• No correlation with complication was reported

• Decision was still done by the surgeon (experience)
Trifecta was defined as a combination of warm ischemia time less than 25 minutes, negative surgical margins and no perioperative complications.

Overall, the quest for trifecta seems to be better accomplished by robotic partial nephrectomy, which is likely to become the new standard for minimally invasive partial nephrectomy.
Perioperative outcome - Nijmegen

Robot partial nephrectomy (2009-2014) n=174

Diameter 3.2 cm (1-9 cm), ≥T1b n=45 (24%)

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<th>Groep &gt;80</th>
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<tbody>
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<td>WI (min)</td>
<td>20 (12-45)</td>
<td>16 (10-34)</td>
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<tr>
<td>BV (ml)</td>
<td>250 (10-1900)</td>
<td>100 (5-600)</td>
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<td>OK duration (min)</td>
<td>234 (121-294)</td>
<td>174 (122-225)</td>
</tr>
<tr>
<td>Console time (min)</td>
<td>160 (70-230)</td>
<td>120 (70-210)</td>
</tr>
</tbody>
</table>
### Outcome - Nijmegen

<table>
<thead>
<tr>
<th></th>
<th>Groep ≤80</th>
<th>Groep &gt;80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kreat pre/post</td>
<td>82 (42-152)</td>
<td>76 (44-374)</td>
</tr>
<tr>
<td></td>
<td>89 (44-163)</td>
<td>90 (52-411)</td>
</tr>
<tr>
<td>Pos. RV</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

PA:
- clearcell 51%
- Papillairy 18%
- Chromofob 5%
- Benign/oncocytoma 22%
- other 4%
Focus on Imaging

CAIX-Immunohistochemistry vs CAIX spect scan

Mulders, Eur. Urol, 2014
Focus on Imaging

- **CA9 (G250)-SCAN** adds biological information to anatomical information
Intraoperative imaging in RCC

Improve radical tumor resection and preserve maximum renal function

- **Partial nephrectomy**
  - Avoid positive resection margin (18% in imperative indications)
  - Visualisation of total intrarenal tumors
  - Preserve normal kidney parenchyma
  - Shorter ischemic interval $\rightarrow$ improved renal function

- **Radical nephrectomy**
  - Visualize metastatic lymph nodes

- **Metastasectomy/local recurrence**

$\rightarrow$ CAIX targeted PET/SPECT imaging using radiolabeled girentuximab

Hekman, Mulders eta, Clin Cancer Res, 2016
Hypothesis: Intraoperative dual-modality imaging may guide the surgeon to tumorous tissue and help to distinguish tumor from normal tissue.
Mouse with an i.p. growing ccRCC tumor lesion, 48 hours after injection of dual-labeled girentuximab.
Challenges in translation

Difficulties in translation to the human situation

- Antigenic make-up
- Vascularization
- Size ratios
- Sensitivity of preclinical imaging systems

→ *Ex vivo* perfusion of human tumorous kidneys (n= 5 kidneys with RCC)
→ Imaging using preclinical and clinical imaging systems

**Aim:**
to assess the feasibility of dual-modality imaging for RCC using Indium-111-girentuximab-IRDye800CW *ex vivo*
Aim: To assess the feasibility and safety of intraoperative dual-modality imaging with $^{111}$In-DOTA-girentuximab-IRDye800CW in renal cancer
Dual-modality imaging of ccRCC

Large clear cell renal cell carcinoma in upper pole of the left kidney

Photo

Fluorescence image (Odyssey)

Autoradiography
RCC tumor thrombus

H&E staining

Fluorescence imaging

CAIX staining

Autoradiography
Pre-operative imaging

- Male, 59 years
- Renal tumor
- Robot-assisted laparoscopic partial nephrectomy
Imaging with $^{111}$In-girentuximab
\textsuperscript{111}In-girentuximab SPECT-CT

- High accumulation in renal tumor
- Physiological accumulation in liver
Dual-modality imaging

- Before tumor resection
- After tumor resection
- On the bench

Tumor ‘on the bench’  Intraoperative liver view
Laparoscopic set-up: Fluorescent and visible light image of tumor border
Ex vivo MRI
T1 weighted  
T2 weighted  
Diffusion weighted
Conclusions

• Increase in SRM detection

• When compared with open surgery, laparoscopic partial nephrectomy is oncologically safe

• The higher complication rate initially reported for laparoscopic partial nephrectomy decreases with increasing surgical expertise

• Partial nephrectomy transfers QOL benefits becoming obvious for laparoscopic vs. open radical surgery to the organ-preservation approach

• The advantage of robot-assisted laparoscopic surgery proven so far is a shorter warm ischemia time and improvement in high renal or Padua score tumors

• Irresistible Rise of Minimally Invasive Treatments in Localized RCC
Thank you

Congress

Personalized Cure and Care in Urology
50 Years of Academic Urology in Nijmegen

In 50 years, the three chairs of the urology Department of the Radboud university medical center, Nijmegen and its co-workers have brought us where we are now: On top of urologic care and cure.

As of 1965 the Department of Urology of the Radboud university medical center achieved its academic standing. Now we are ready for the next step. Would you like to know what this step will be? Join us on September 11, 2015 at the Congress Personalized Cure and Care in Urology in Nijmegen, The Netherlands. Our steps to the future of urology will be presented. Enjoy several national and international keynote speakers delivering state-of-the-art lectures on current issues at the Radboud university medical center.