

Debate: Lymphadenectomy is Important in mRCC, CON

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.



The role of LND

- In organ confined tumors
- In locally advanced or high risk RCCs
- In metastatic RCC

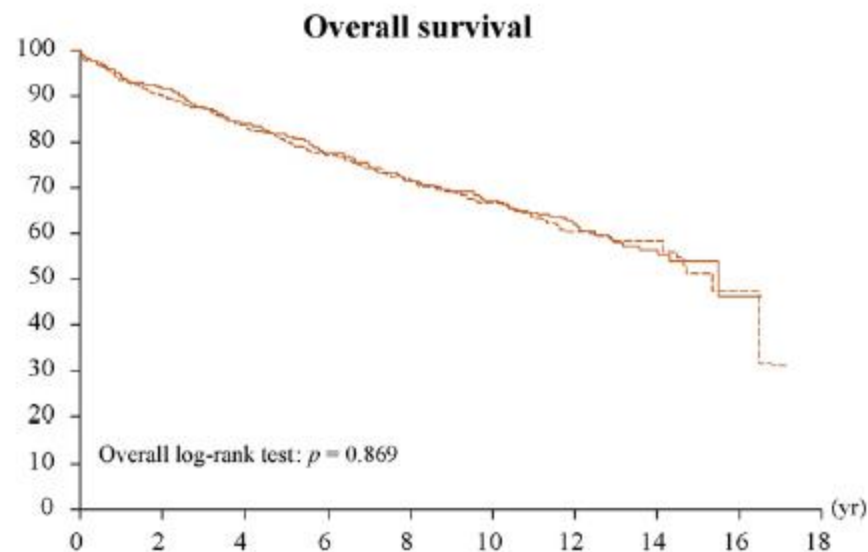
The role of LND in organ confined tumors



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

Jan H.M. Blom^{a,*}, Hein van Poppel^b, Jean M. Maréchal^c, Didier Jacqmin^d, Fritz H. Schröder^e, Linda de Prijck^f, Richard Sylvester^f, for the EORTC Genitourinary Tract Cancer Group

	Without lymph-node dissection		With complete lymph-node dissection	
	n	%	n	%
Site of the tumor				
Right side	195	53	198	54
Left side	172	47	169	46
Tumor category				
T1	23	6	34	9
T2	242	66	221	60
T3	101	28	112	31
Tumor diameter, cm				
Median	6		5.5	
Maximum	20		19	



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

Cause of death	Without lymph-node dissection (n = 389)	With complete lymph node dissection (n = 383)
Alive	254 (65%)	246 (64%)
Malignant disease	67 (17%)	68 (18%)
CVD	28 (7%)	29 (8%)
Other/unknown	40 (10%)	40 (10%)

CVD = cardiovascular disease.

	Without lymph-node dissection (n = 389)	With complete lymph-node dissection (n = 383)	Hazard ratio	95% confidence interval	p value
Death	135 (35%)	137 (36%)	1.02	0.80–1.29	0.87
Local regional progression	34 (9%)	26 (7%)	0.77	0.46–1.28	0.31
Distant progression	58 (15%)	60 (16%)	1.05	0.73–1.50	0.81
Local or distant progression	93 (24%)	87 (23%)	0.95	0.71–1.27	0.70
Progression or death	156 (40%)	159 (42%)	1.02	0.82–1.28	0.84
Second primary	45 (12%)	36 (9%)	0.79	0.51–1.22	0.28

There is no place for LND in organ confined RCC

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*

Recommendations	Grade
For T1 RCCs, nephron-sparing surgery should be performed whenever possible. Open partial nephrectomy currently remains the standard.	A
Laparoscopic radical nephrectomy is recommended in T2 renal cell cancer when nephron-sparing surgery is not suitable.	B
Extended lymphadenectomy does not improve survival and can be restricted to staging purposes.	A

In patients with palpable or CT-detected enlarged lymph nodes, resection should be performed to obtain adequate staging information

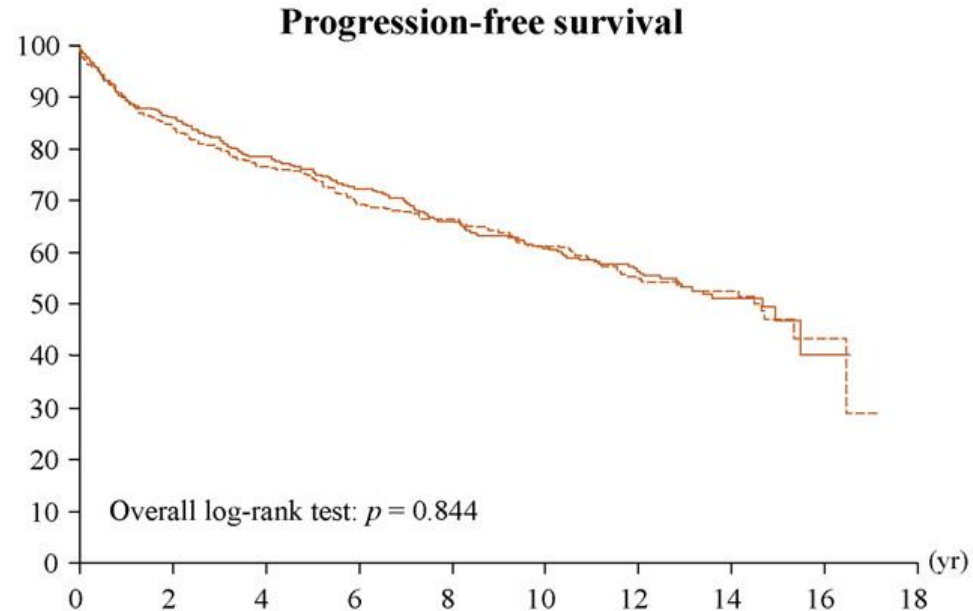
The role of LND in locally advanced RCC

**Eighth European International
Kidney Cancer Symposium**
Budapest – 03-04 May 2013



Role of LND in locally advanced RCC

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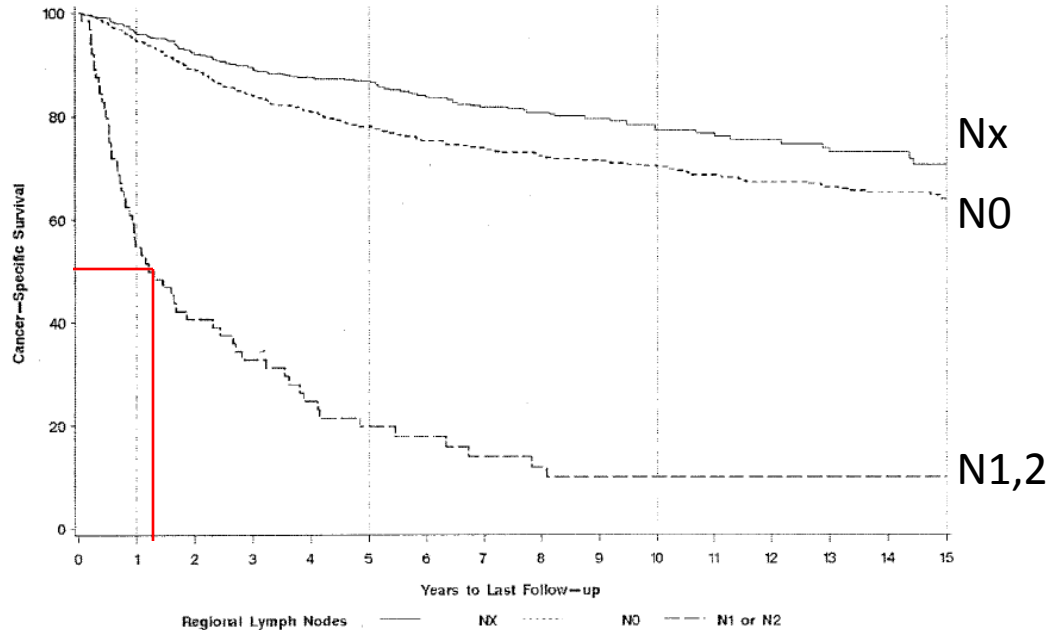


The study was not powered for showing a difference in T stage subgroups

LND in locally advanced RCC

- Enlarged LN at CT is not synonym for node metastases:
 - In 58% of the enlarged nodes at CT final pathology showed only inflammatory changes and/or follicular hyperplasia. This finding was significantly more frequent in patients with tumor involvement of the renal vein and tumor necrosis.
- In high-risk patients (cT3–T4N0 or cTany, N1-2), the majority of the retrospective nonrandomized trials suggest a possible benefit of regional LND on CSS
 - Selection biases? Studer et al., J Urol 1990
 - How to select patients who are at risk of LNI Pantuck et al., J Urol, 2003
Blute et al., J Urol, 2004
Delacroix et al., J Urol, 2011
Capitanio et al., Eur Urol 2011

Biases from retrospective studies



stage pN0 tumors were significantly more likely to die of renal cell carcinoma than those with stage pNx tumors (risk ratio 1.40, p 0.003).

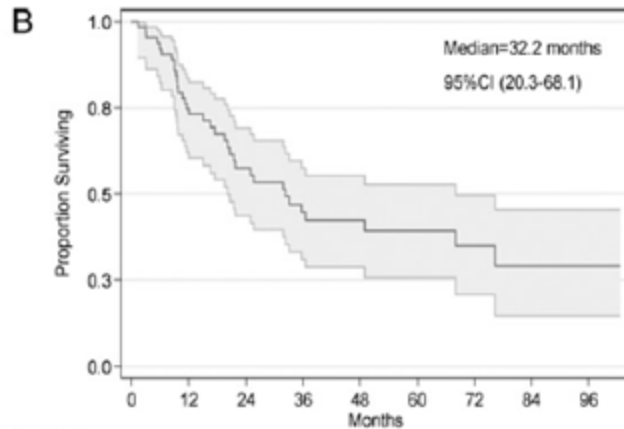
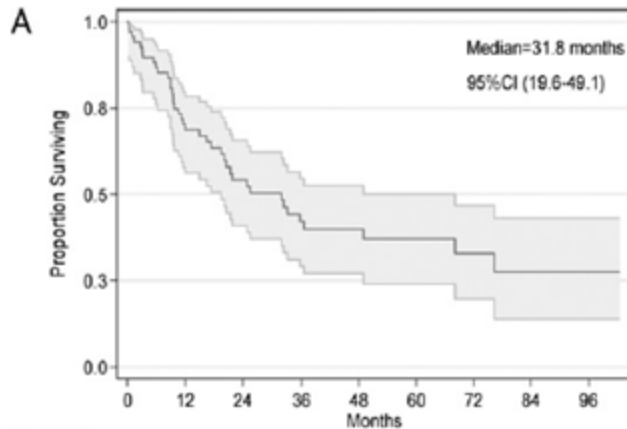
Increasing the extent of LND does not improve CSS in all retrospective studies

- In multivariable analyses (n = 7680), increasing extent of LND failed to predict CSM in pN0 patients (HR, 0.89, 95% CI, 0.75–1.04; P = 0.1)
- Similarly, among patients with the presence of positive lymph nodes, increasing the extent of LND (per 10 node increase) did not achieve independent predictor status (HR, 0.83, 95% CI, 0.66–1.05; P = 0.1).

Can a Durable Disease-Free Survival be Achieved With Surgical Resection in Patients With Pathological Node Positive Renal Cell Carcinoma?

Yes, but patients at risk must be identified for avoiding 97% unnecessary LND

- 2,521 patients (T any, N any, M0)
- 68 patients (2.7%) with N1-2 stages
- 5-year OS and DSS were 37% and 39%,
- 5.6% of the patients with LND died within the first 60 days after surgery



Retrospective data, no comparative group with no LND

Delacroix et al., J Urol 2011

Conclusion of the unique randomized study on LND in RCC

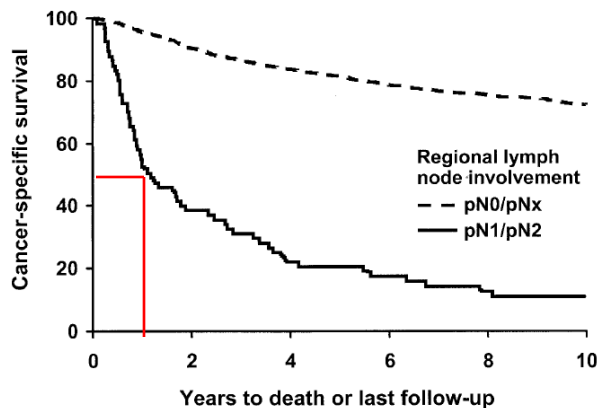
- This does not mean that a lymph-node dissection should be completely abandoned.
- In cases of aggressive cancer, patients may benefit from lymph-node dissection.
- It will, however, be difficult to identify those individual patients.

A PROTOCOL FOR PERFORMING EXTENDED LYMPH NODE DISSECTION USING PRIMARY TUMOR PATHOLOGICAL FEATURES FOR PATIENTS TREATED WITH RADICAL NEPHRECTOMY FOR CLEAR CELL RENAL CELL CARCINOMA

1,652 patients who underwent RN for M0 RCC: 3% pN1, 1% pN2

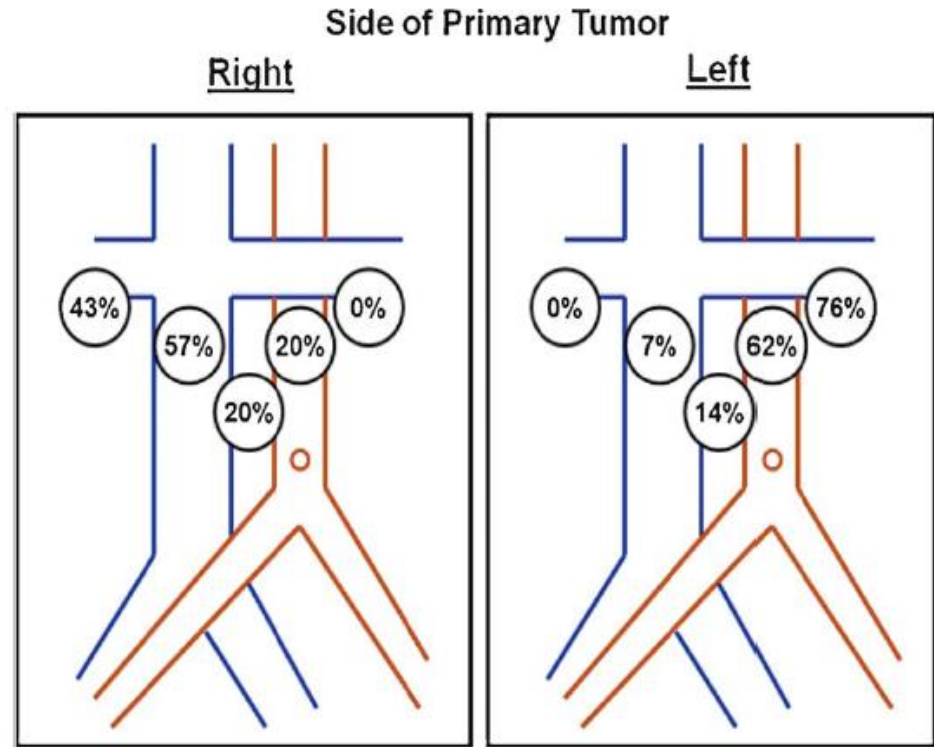
Feature	Odds Ratio (95% CI)	p Value
Nuclear grade: 1 + 2	1.0 (reference)	
3 + 4	5.25 (1.99–13.82)	<0.001
Sarcomatoid component	4.11 (2.08–8.12)	<0.001
Tumor 10 cm or greater	2.17 (1.27–3.70)	0.005
Primary tumor stage: pT1 + pT2	1.0 (reference)	
pT3 + pT4	2.00 (1.13–3.55)	0.017
Histological tumor necrosis	1.86 (1.00–3.48)	0.051

No. Features	No. pN0/pNx (%)	No. pN1/pN2 (%)
Total pts	1,584	68
0	726 (99.6)	3 (0.4)
1	299 (99.0)	3 (1.0)
2	264 (95.7)	12 (4.4)
3	183 (87.6)	26 (12.4)
4	105 (86.8)	16 (13.2)
5	7 (46.7)	8 (53.3)



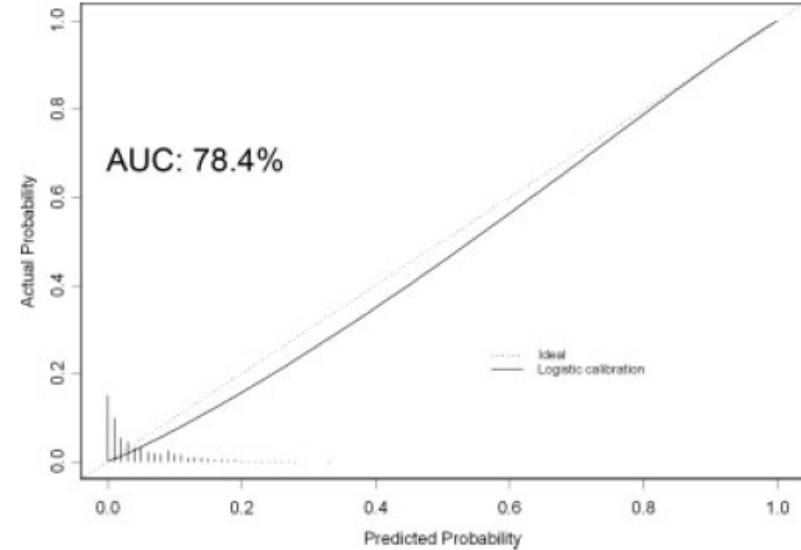
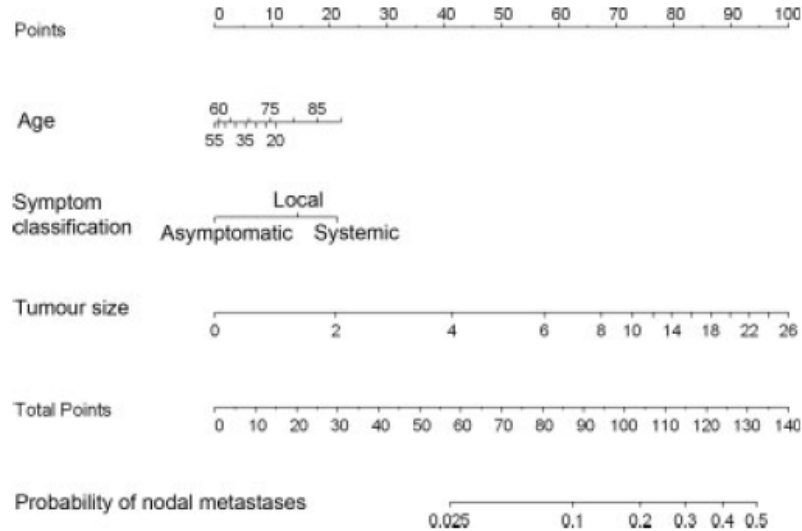
Template of LND in high risk RCC patients

- 415 radical nephrectomies for M0 patients
- Of the 169 high-risk patients, 64 (38%) had LN metastases.
- **It means: 62% unnecessary LND**



Patients with renal cell carcinoma nodal metastases can be accurately identified: External validation of a new nomogram

Georg C. Hutterer^{1,2}, Jean-Jacques Patard³, Paul Perrotte⁴, Constantin Ionescu¹, Alexandre de La Taille⁵, Laurent Salomon⁵, Gregory Verhoest³, Jacques Tostain⁶, Luca Cindolo⁷, Vincenzo Ficarra⁸, Walter Artibani⁸, Luigi Schips², Richard Zigeuner², Peter F. Mulders⁹, Antoine Valeri¹⁰, Denis Chautard¹¹, Jean-Luc Descotes¹², Jean-Jacques Rambeaud¹², Arnaud Mejean¹³ and Pierre I. Karakiewicz^{1,4*}

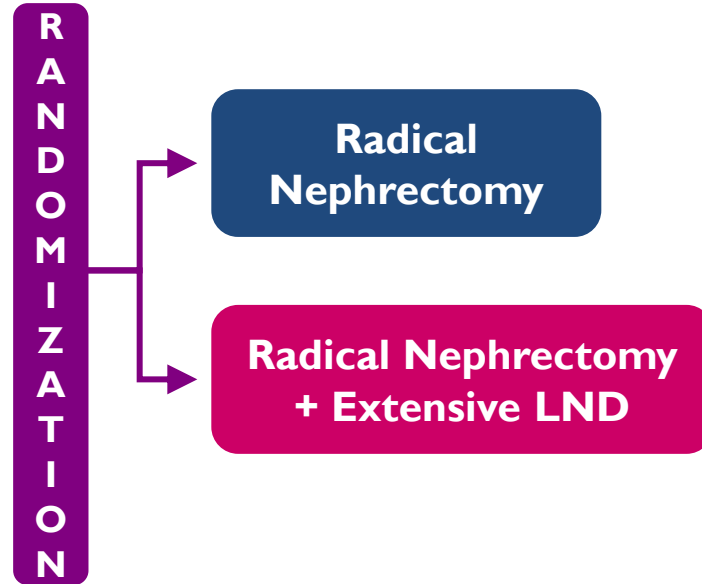


Need for a randomized study in high risk M0 RCC patients

High Risk M0 RCC patients

≥ 2 of the following features

- nuclear grade ≥3
- sarcomatoid component,
- tumor size ≥10 cm,
- tumor stage ≥T3
- coagulative tumor necrosis.

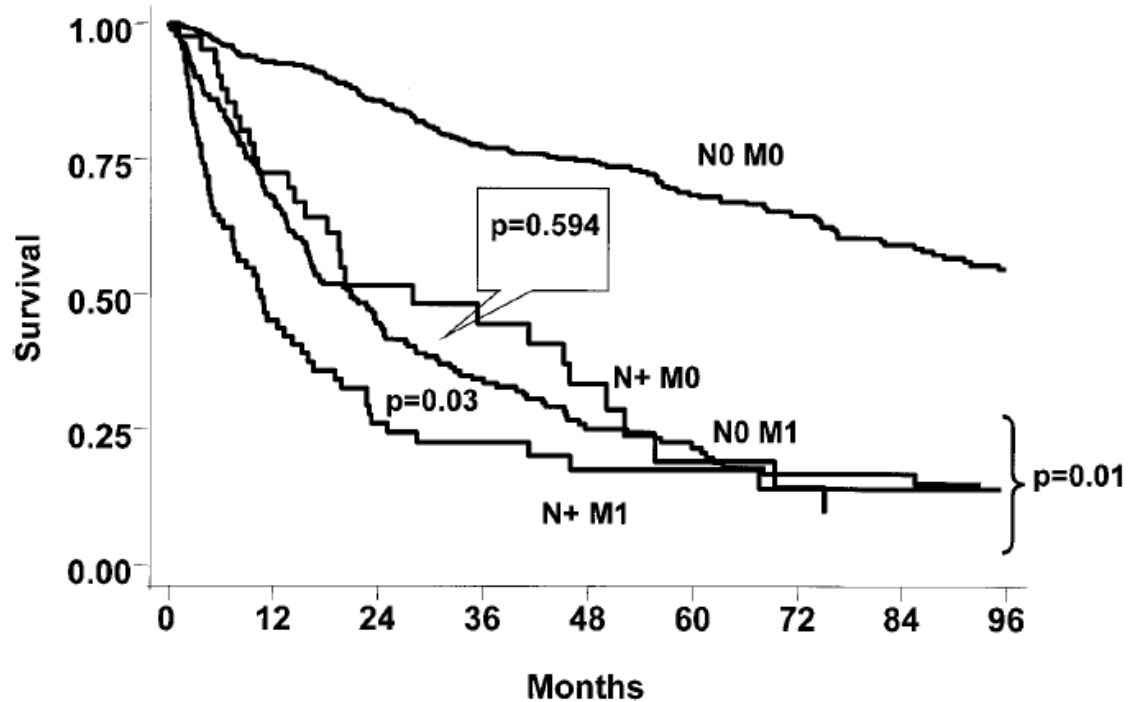


Primary End Point : OS

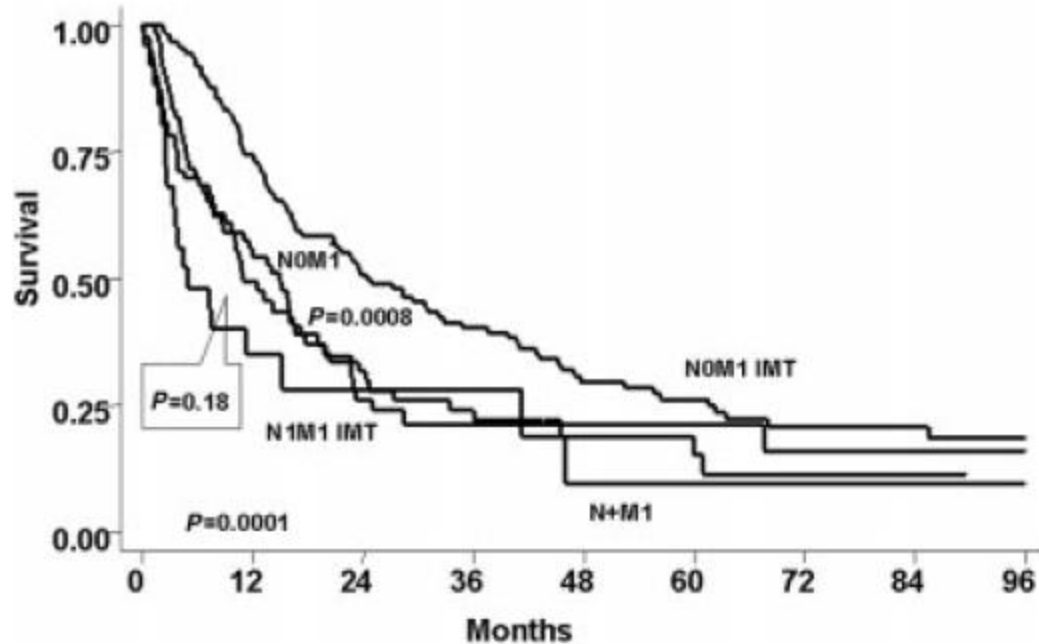
LND in metastatic RCC



Survival in N1N2 stages is the same than in M1 stage

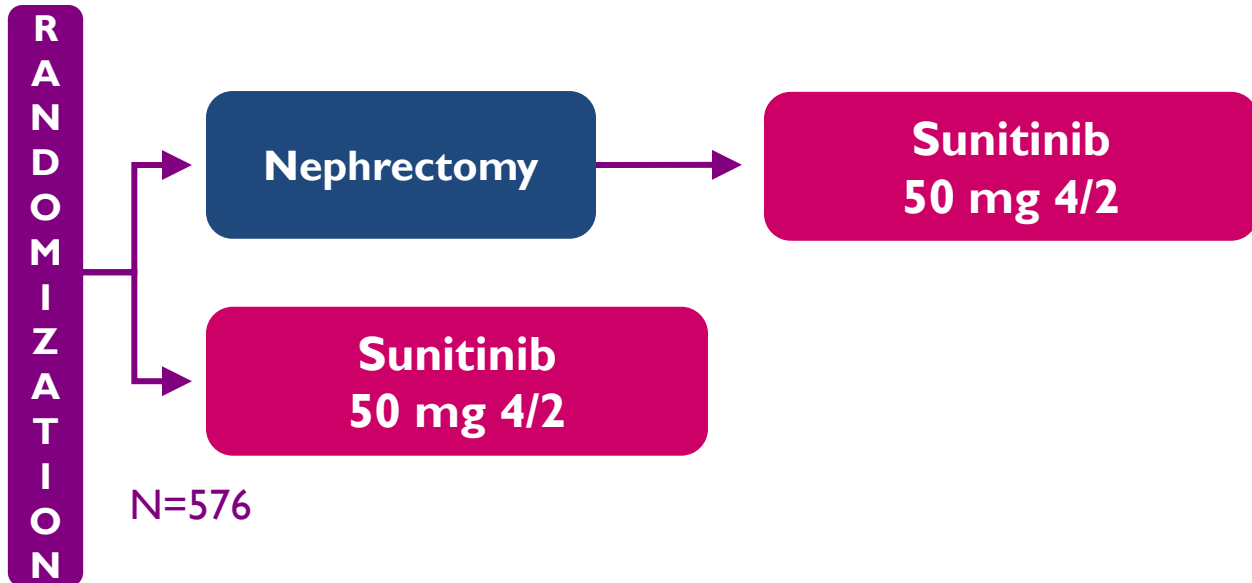


No influence of systemic treatment in the era of IMT



The role of nephrectomy in mRCC in the era of targeted therapy is not established
The issue of the role of LND has not been prospectively addressed
Phase 3 Randomized Study Comparing Nephrectomy Plus Sunitinib vs Sunitinib Without Nephrectomy in First-Line Metastatic RCC

Carmena trial



CARMENA Study, PI: Pr Arnaud Mejean (CCAFU – HEGP Hospital – Paris, France)



conclusions

- It is established that LND is not required in organ confined RCC
- Some progress has been made in identifying high risk patients for LN invasion
 - There is currently no robust evidence suggesting that extensive LND improves survival in this setting
 - There is a need for a randomized study in this setting
 - We still need to improve the accuracy of predictive models for LNI
- Regarding mRCC we first have to demonstrate that nephrectomy is useful.
 - We should have stratified for LND
 - We won't have the response about the utility of LND unless we design a specific trial addressing this issue