14:05-14:20

Surgery has a role in Node-Only M1 UC

La cirugía tiene un papel en pacientes con carcinoma urotelial y afectación ganglionar metastásica exclusiva

Dr. José Rubio, Servicio Urología, Hospital Universitario Vithas 9 de Octubre, Valencia

Dr. J. Rubio Briones

Director Servicio Urología. Hospitales VITHAS, Valencia

Presidente de Surg For All

Guión

- 1.- Potenciales mejorías estadiaje ganglionar
- 2.- Manejo ganglios si empezamos 1º por Cirugía:
  - En la Cistectomía
  - En la Preservación
- 3.- Manejo ganglios si empezamos 1º por Tratamiento sistémico:
  - Neo-adyuvancia
  - QT por cN_{1-3}
- 4.- Nuevas líneas ante cN+

Potenciales mejorías en el estadiaje ganglionar

N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in a common iliac lymph node(s)

cTxN2-3 & cTxM1a

^{18}F-FDG PET-TAC & estadiaje

711 TVMI ; 1º TAC T-A-P + 2º PET-TAC FDG

- Cambio estadiaje: 26%
  - Sobre estadiaje : 25%
  - 44% cM1a sobrestadiados a cM1b
  - 28% cN1-3 sobrestadiados a cM1a-b
- Cambio estrategia: 18%
  - Curativa a paliativa: 9.1%
- Indicación neoady. por PET TAC FDG; 7%
- 2º primario ; 15% (!8% falsos positivos!)

Voskuilen et al. Eur Urol Oncol 2022; 366-69

Consenso Delphi para definición TV OligoM+

- Consideración ganglios como un órgano, pero 3 localizaciones:
- Pélvicos / Retroperitoneo / Supradiafragmáticos
- NO Consenso:
  - cómo considerar los ganglios pélvicos
  - Uso del PET-TAC FDG como estadiaje

Bamias et al. Eur Urol 2023; 84: 381-89

cN: GUIAS 2025; PET TAC FDG

Rol por aquilatar

No uso rutinario

La mayoría estudios demuestran:

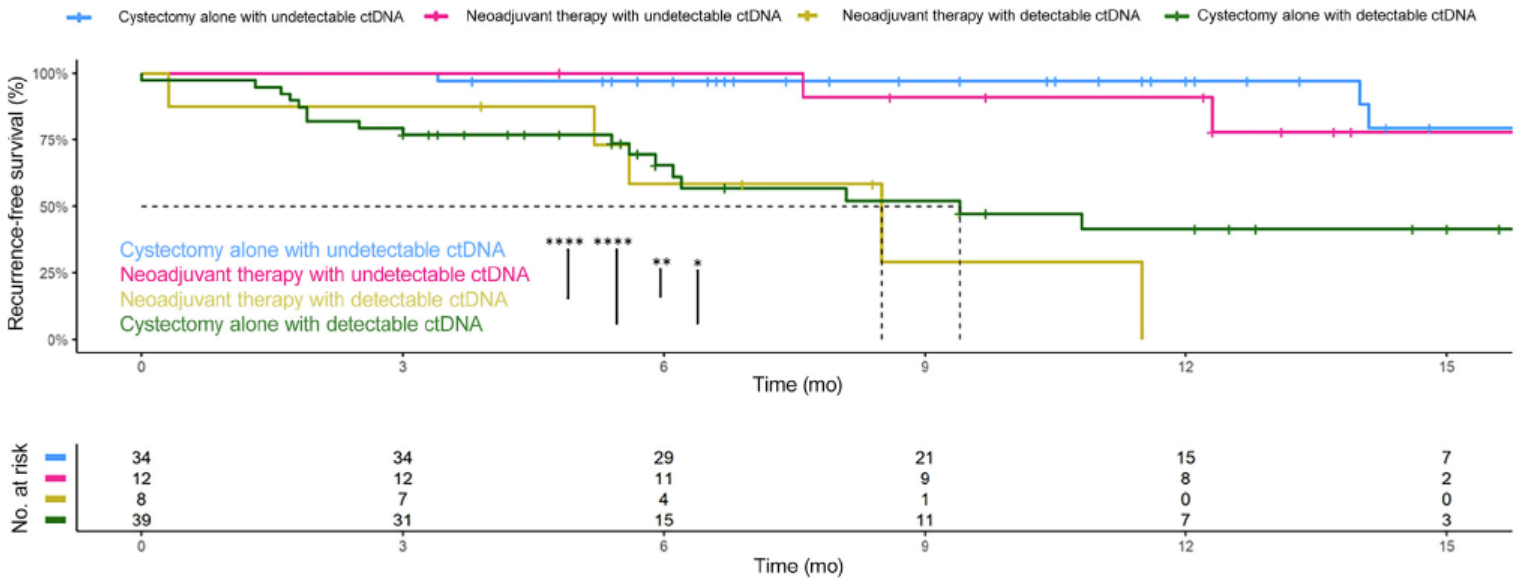
- Mejores estadísticos que la TAC
- 20% de microM+ ganglionares NO detectadas
- Sobrestadiaje 20%

Nuevos trazadores en estudio;

- 64CuCl2,
- [68Ga]Ga-FAPI-46 (*fibroblast activation protein*)
- 68Ga-FAP-2286

Guias Clínicas EUA 2025

ct DNA pre CR & pN/pT y SLR



	Recurrence-free survival at 6 mo	Recurrence-free survival at 12 mo
Cystectomy alone with undetectable ctDNA	97%	97%
Neoadjuvant therapy with undetectable ctDNA	100%	91%
Neoadjuvant therapy with detectable ctDNA	58%	29%
Cystectomy alone with detectable ctDNA	66%	47%

Ben-David et al, Eur Urol Oncol 2024; 7: 1105-1112

ct DNA pre y pN/pT

Table 2 – Univariable and multivariable analyses for LN⁺ disease and locally advanced disease (≥pT3) on final pathology

Parameter	N	Events	Univariable			Multivariable	
			OR (95% CI)	*p* value	*q* value	OR (95% CI)	*p* value
LN⁺ disease							
VH on TURBT (vs no)	108	29	3.3 (1.3–8.5)	**0.014**	**0.014**	3.4 (1.2–10)	**0.02**
≥cT2 stage (vs <cT2)	109	29	3.6 (1.3–11.4)	**0.011**	**0.014**	2.7 (0.9, 9.4)	0.1
Precystectomy detectable ctDNA(vs undetectable)	109	29	6.8 (2.5–22)	**<0.001**	**<0.001**	5.4 (1.9–18.2)	**0.003**
≥pT3 disease							
Age	112	44	1.06 (1.02–1.12)	**0.005**	**0.008**	1.04 (0.99–1.11)	0.1
Female sex (vs male)	112	44	1.5 (0.6–4)	0.39	0.49	1.6 (0.5–4.7)	0.4
VH on TURBT (vs no)	111	44	1.3 (0.5–3.1)	0.56	0.56	1.1 (0.4–3.1)	0.8
≥cT2 stage (vs <cT2)	112	44	5 (2–13.6)	**<0.001**	**<0.001**	3.6 (1.4–10.2)	**0.013**
Precystectomy detectable ctDNA(vs undetectable)	112	44	4.9 (2.1–11.6)	**<0.001**	**<0.001**	3.6 (1.5–9)	**0.005**

OR = odds ratio; CI = confidence interval; ctDNA = circulating tumor DNA; LN⁺ = lymph node–positive; TURBT = transurethral resection of bladder tumor; VH = variant histology.

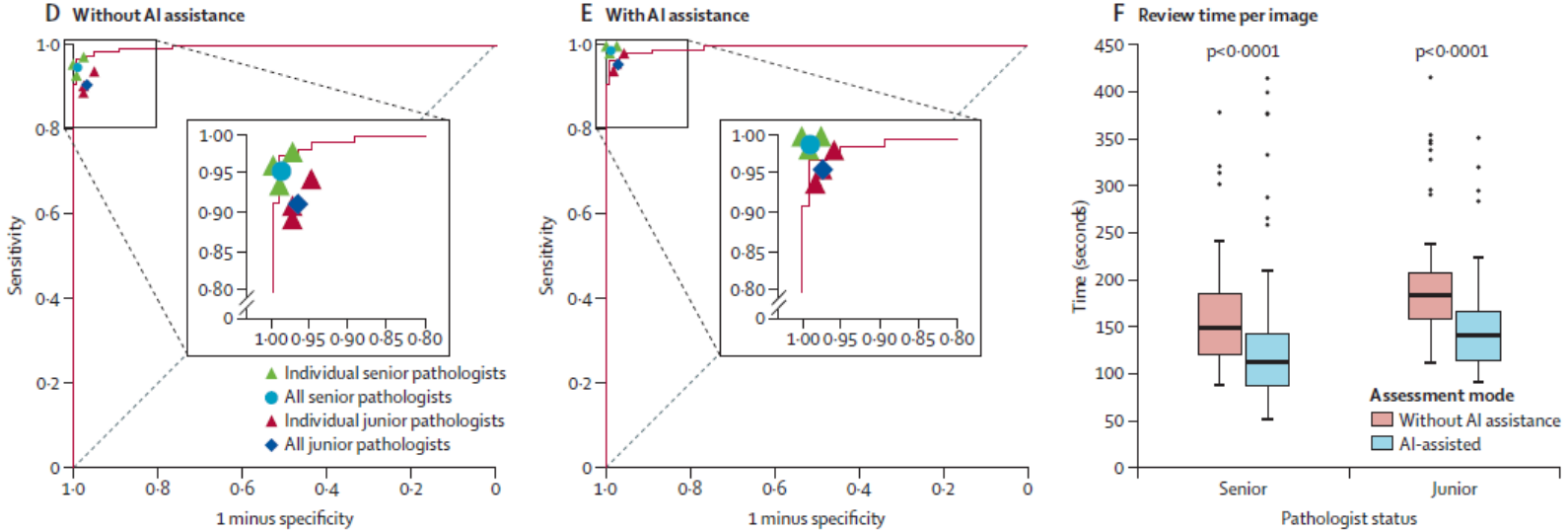
*** of the 29 patients in our study with node-positive disease, ten (34%) experienced ctDNA clearance to undetectable status in the MRD window before receiving adjuvant treatment. None of these patients experienced recurrence.

*** If longer follow-up confirms these results, and if supported by future clinical trials, patients with similar characteristics might be able to avoid adjuvant treatment., While patients with detectable ctDNA before surgery could gain an additional survival benefit from a superextended lymph-node template.

Ben-David et al, Eur Urol Oncol 2024; 7: 1105-1112

IA & diagnóstico AP de M+ ganglionares

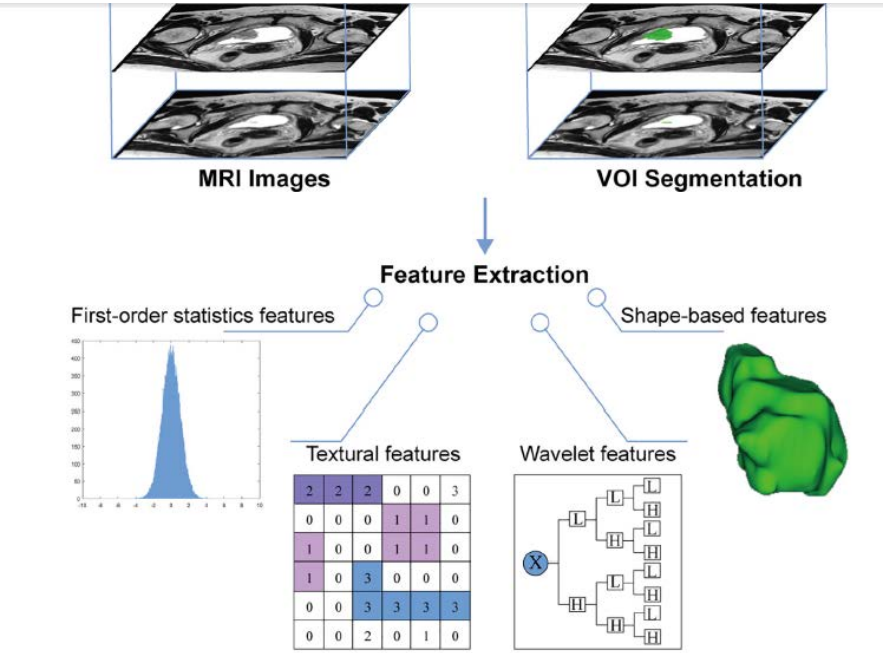
Artificial intelligence-based model for lymph node metastases detection on whole slide images in bladder cancer: a retrospective, multicentre, diagnostic study

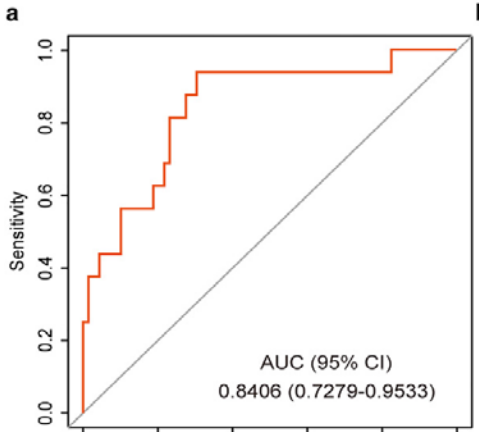


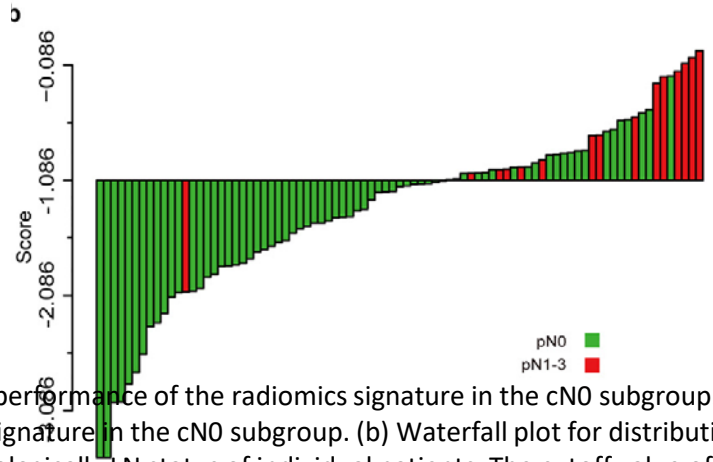
Mejor precisión + mayor rapidez + 80-92% slides no necesarias a revisar
Buena sensibilidad (+9%) & aplicabilidad y automatización

Wu et al, Lancet Oncol 2023; 24: 360–70

IA & diagnóstico por RM de M+ ganglionares





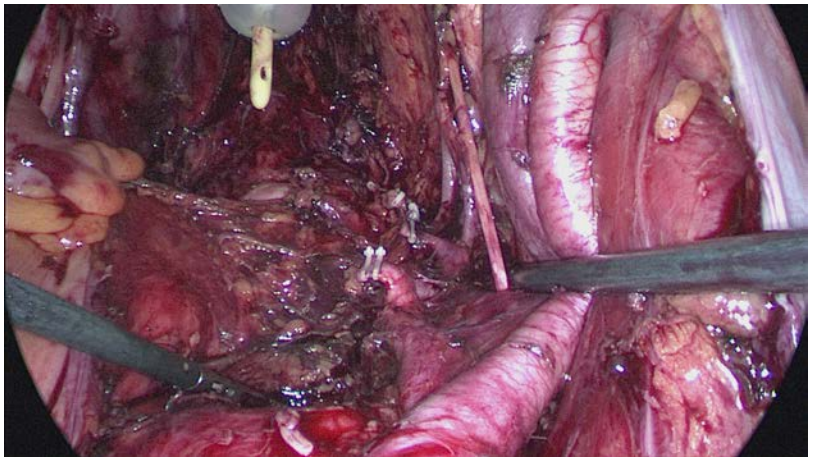


4 categorías de datos radiómicos

Wu et al, EBIoMedicine 2018

The predictive performance of the radiomics signature in the cN0 subgroup. (a) ROC curve of the radiomics signature in the cN0 subgroup. (b) Waterfall plot for distribution of radiomics score and pathologically LN status of individual patients. The cutoff value of the radiomics score was −1.086.

Manejo ganglios si empezamos 1º por Cirugía: Cistectomía + LDN



SLP CR sin neo ni adyuvancia

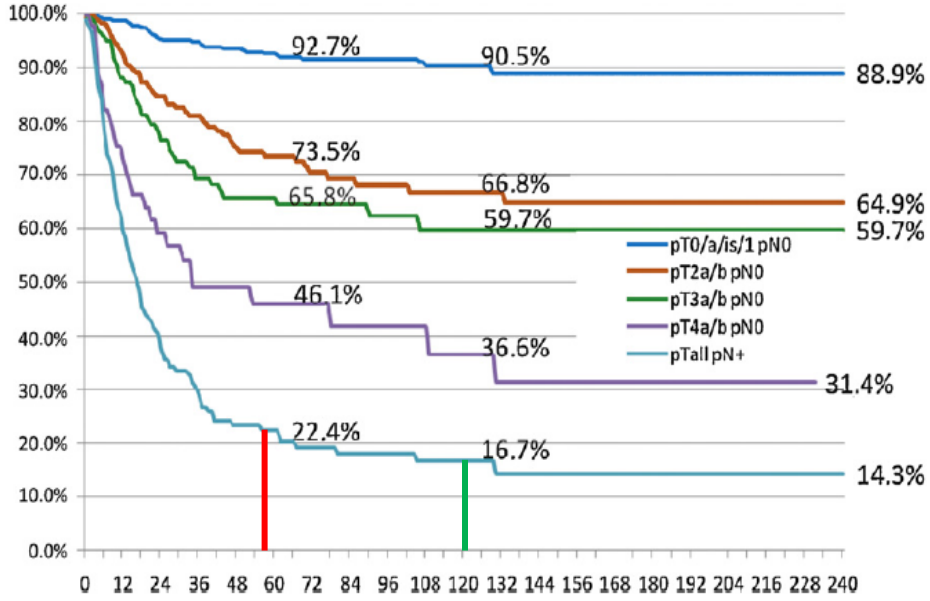
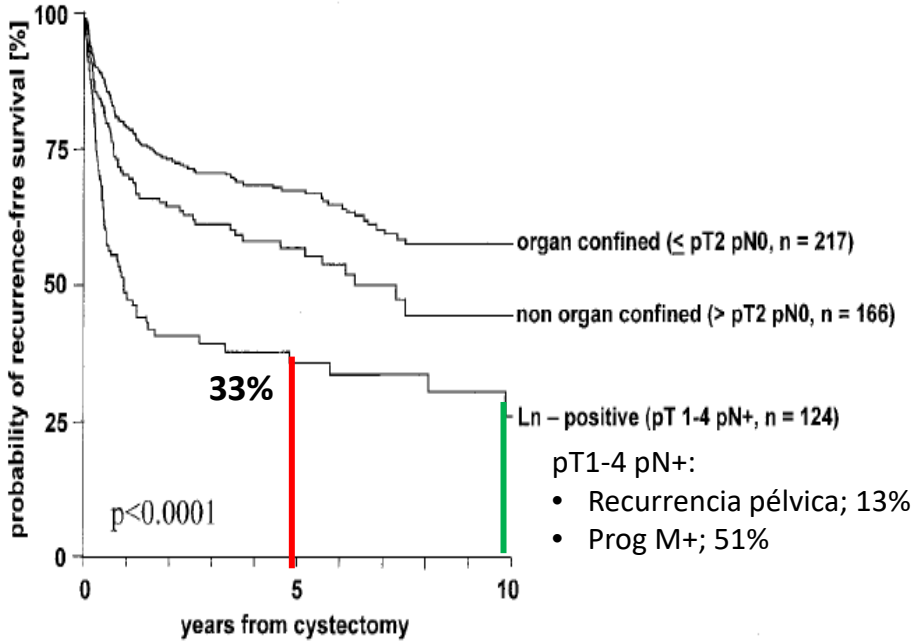


Fig. 2 – Disease-specific survival rates according to the tumor stage of the cystectomy specimen.



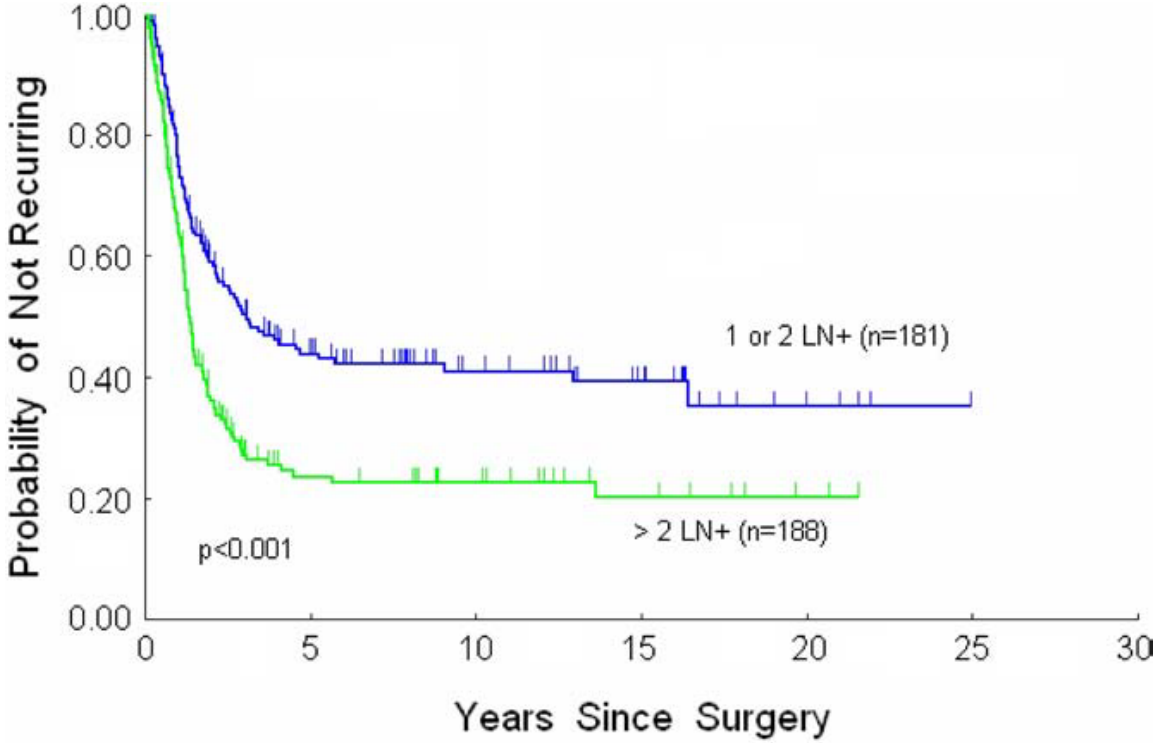
pT1-4 pN+:

- Recurrencia pélvica; 13%
- Prog M+; 51%

(U. Ulm) Hautmann et al, Eur Urol 2012

(U. Berna) Madersbacher et al, Clin Oncol 2003

Supervivencia pN+ tratados con CR+LDN



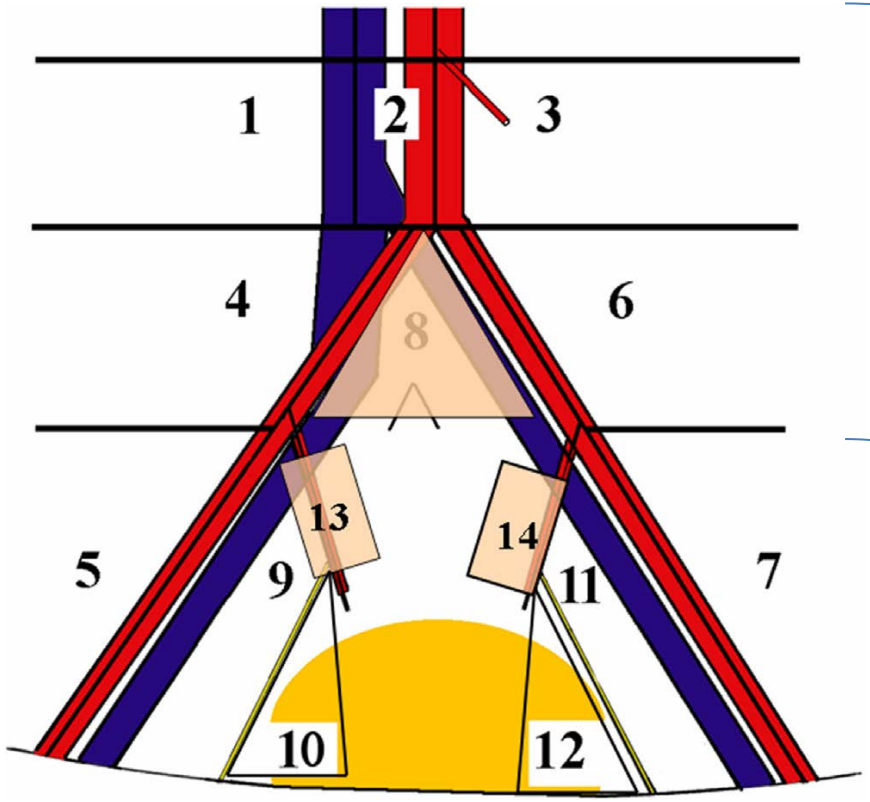
1 o 2 gg afectos (n=181) &
Multivariado para progresión:

- **pT (≤pT2 vs ≥pT3)***
- **LN density (≤4% vs ≥4%)***
- **QT adyuvante (sí vs no)**

* (ídem en ptes con o sin QT peroperatoria)

(UCLA) Bruins et al , J Urol 2009

Fase III Asoc Alemana Uro; Extendida vs limitada



LDN extendida; Limitada +: (n=198)

- Obturadores profundos
- Presacros
- Ilíacos comunes
- Paracavos
- Interaortocavo
- Paraórticos

LDN limitada (n=203)

- obturadores +
- ilíacos internos +
- ilíacos externos

Gschwend, Eur Urol 2019

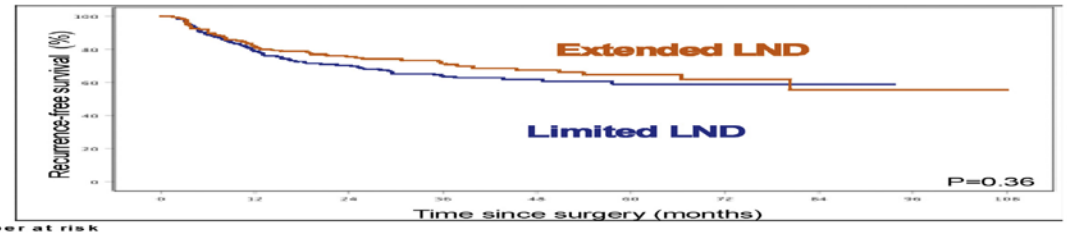
Fase III Asoc Alemana Uro; Extendida vs limitada

- Ganglios + (pN+) en 100 (25%) pacientes
- Mediana gg disecados 19 en LDN limitada y 31 en la extendida (p < 0.001)
- Segto medio; 58m
- No NeoAdyv
- 2% FN -pN0- por LDN limitada
- Tto adyuvante & investigador; 15% en cada rama

Gschwend, Eur Urol 2019

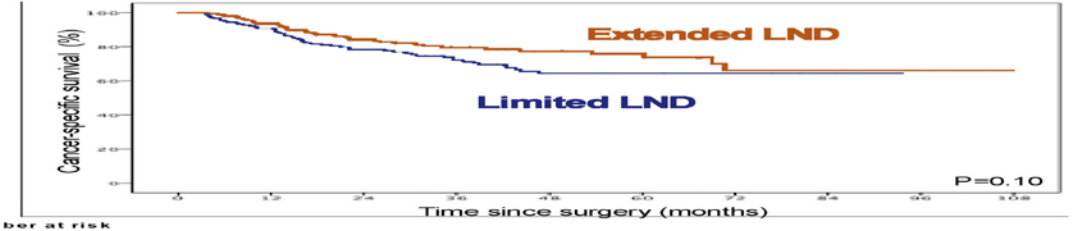
Heck et al, EUA Congress 2023

A Recurrence-free survival



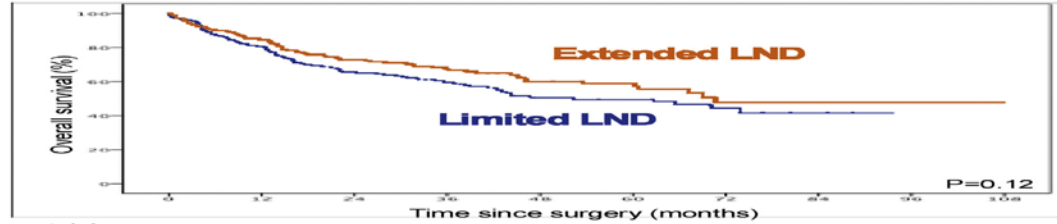
Number at risk										
Extended LND	198	127	108	81	53	34	14	8	1	1
Limited LND	203	127	101	79	54	35	20	6	0	0

B Cancer-specific survival



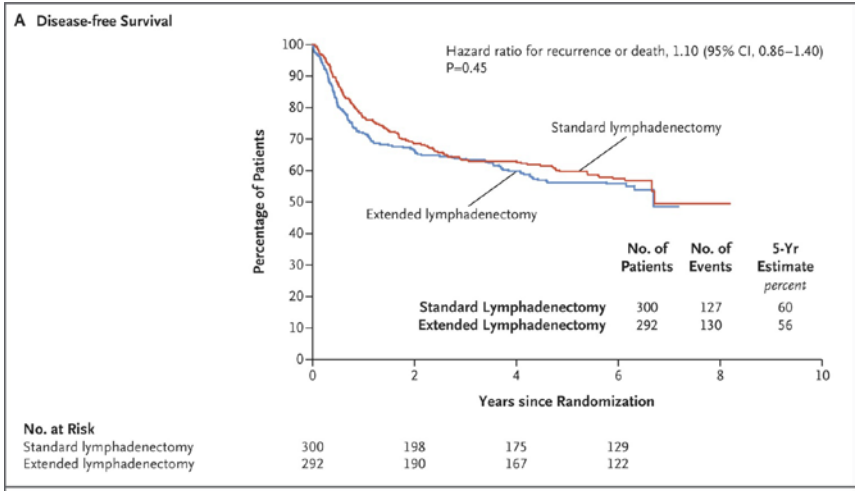
Number at risk										
Extended LND	198	144	119	88	58	37	14	8	1	1
Limited LND	203	145	110	86	55	38	20	6	0	0

C Overall survival



Number at risk										
Extended LND	198	144	119	88	58	37	14	8	1	1
Limited LND	203	145	110	86	55	38	20	6	0	0

Fase III USA SWOG S1011; Extendida vs limitada



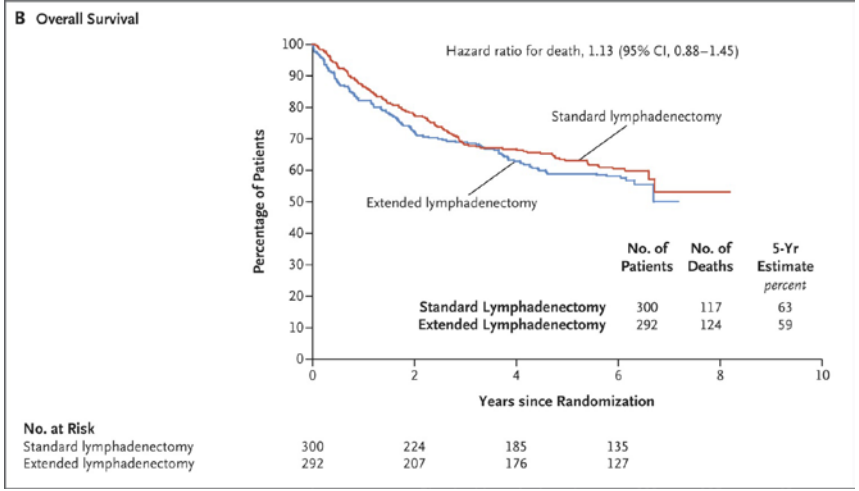


Table 3. Selected Adverse Events of Grade 3 to 5 Occurring within 90 Days after Surgery.*

Event	Standard Lymphadenectomy (N=300)†				Extended Lymphadenectomy (N=292)			
	Grade 3	Grade 4	Grade 5	Grade 3 to 5	Grade 3	Grade 4	Grade 5	Grade 3 to 5
	no. of patients			*no. (%)*	*no. of patients*			*no. (%)*
Anemia	53	1	0	54 (18)	45	0	0	45 (15)
Urinary tract infection	28	0	0	28 (9)	24	1	0	25 (9)
Sepsis	0	12	2	14 (5)	0	19	1	20 (7)
Wound complications	12	0	0	12 (4)	14	1	0	15 (5)
Leukocytosis	7	0	0	7 (2)	11	1	0	12 (4)
Venous thromboembolic event	5	1	2	8 (3)	7	4	1	12 (4)
Ileus	7	0	0	7 (2)	10	2	0	12 (4)
Hyponatremia	8	0	0	8 (3)	6	2	0	8 (3)
Hypertension	8	0	0	8 (3)	9	0	0	9 (3)
Surgical or medical procedure	9	0	0	9 (3)	12	5	0	17 (6)
Acidosis	7	0	0	7 (2)	6	0	0	6 (2)
Hyperkalemia	5	1	0	6 (2)	4	1	0	5 (2)
Dehydration	6	0	0	6 (2)	3	0	0	3 (1)
Hypotension	3	1	0	4 (1)	3	1	1	5 (2)
Respiratory failure	0	1	0	1 (<1)	0	6	1	7 (2)
Myocardial infarction	2	1	0	3 (1)	0	0	3	3 (1)
Death, not otherwise specified	0	0	0	0	0	0	4	4 (1)
Other cardiac event	1	0	0	1 (<1)	0	0	1	1 (<1)
Stroke	1	0	0	1 (<1)	0	0	1	1 (<1)
Aspiration	0	0	0	0	1	0	1	2 (1)
Multiorgan failure	0	0	0	0	0	1	1	2 (1)
Disseminated intravascular coagulation	0	0	1	1 (<1)	0	0	0	0
Ventricular fibrillation	0	0	0	0	0	0	1	1 (<1)
Any adverse event according to maximum grade	107	21	4	132 (44)	116	29	12	157 (54)

* According to the Common Terminology Criteria for Adverse Events, version 4.0, an event of grade 3 is serious, of grade 4 is life-threatening, and of grade 5 resulted in death. Data regarding one death due to multiple surgical complications that occurred in the extended-lymphadenectomy group at 102 days after surgery are included in this table.

† Four patients who had been randomly assigned to the standard-lymphadenectomy group underwent extended lymphadenectomy after standard lymphadenectomy was initially attempted. These patients were included in the standard-lymphadenectomy group for this analysis.

Lerner et al ; N Engl J Med 2024;391:1206-16

Papel de la CR+LDN como monoterapia en adenopatías macroscópicas (cT_{1-4} N_{2-3})

¿ Se debe continuar la CR si se encuentran N+ “pasadas” (pN2-N3)?

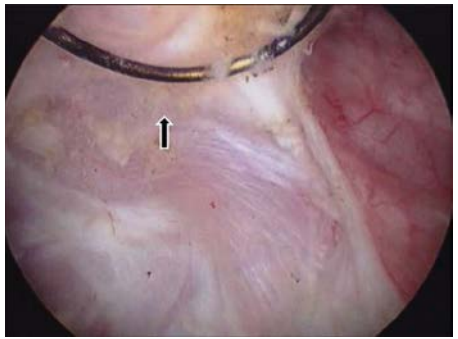
- N=84 casos (10 años segto)
- **24%** (20 pacientes) **sobrevivieron media 10 años**
- Mejor en subgrupos ≤pT_2
- 76% mueren por tumor; supervivencia 19m
- Concluyen; control síntomas pélvicos + “chance” de sobrevivir un 24%

Herr et al J Urol 2001; 165: 62-64

- Si se “aborta” la CR+LDN ante gg macro +; SG 0-9% tras QT en 5 años

Guzzo et al BJU Int 2008; 102: 1539-42, Yafi et al, Urol Oncol 2001; 29: 309-13

Manejo ganglios si preservamos vejiga: Preservación + LDN



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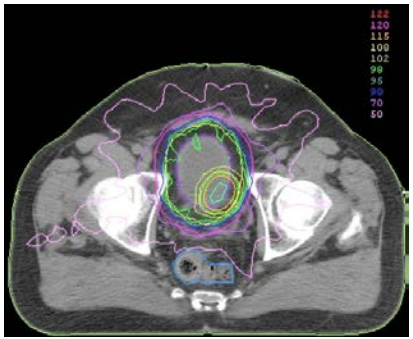
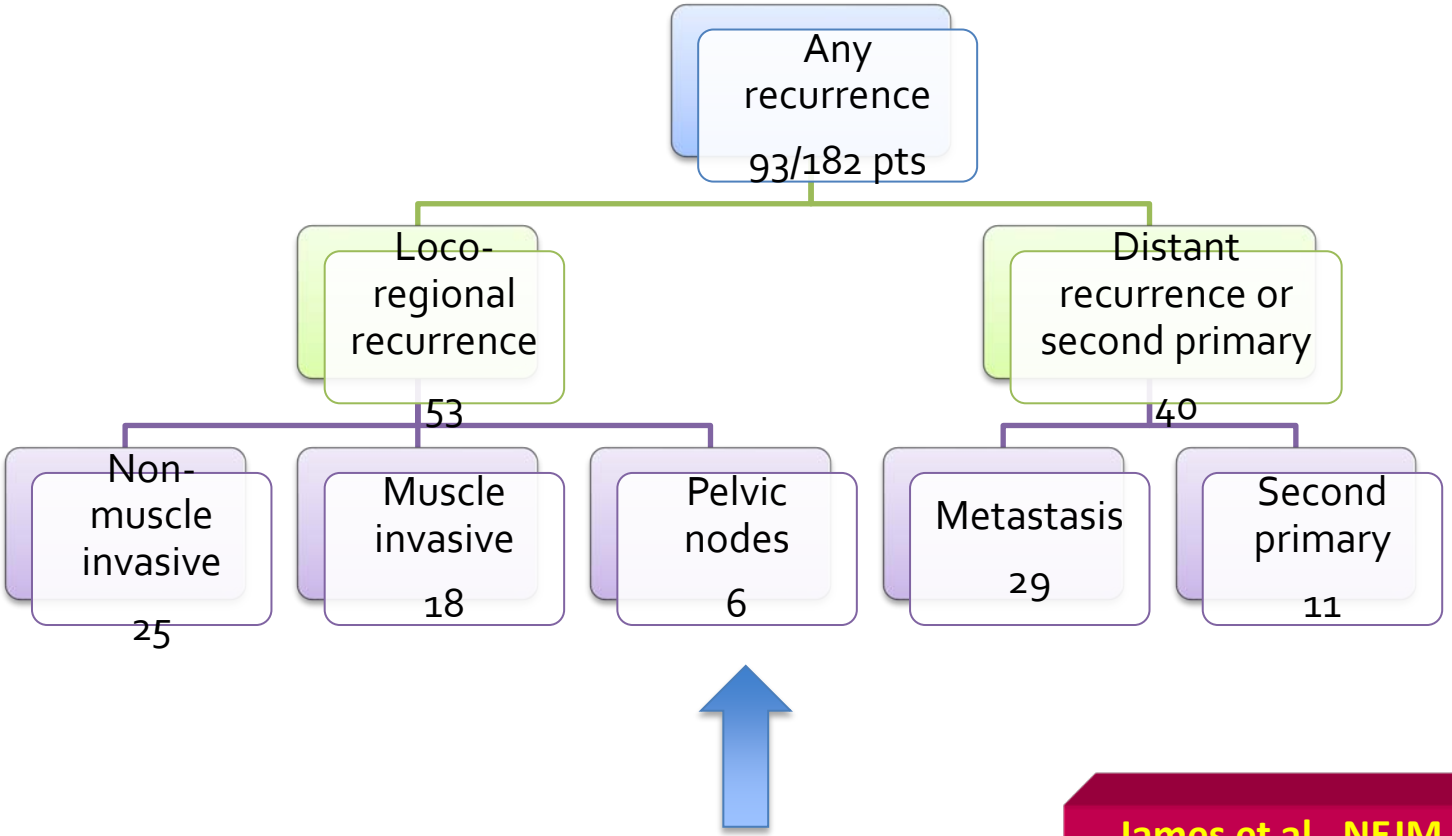


+

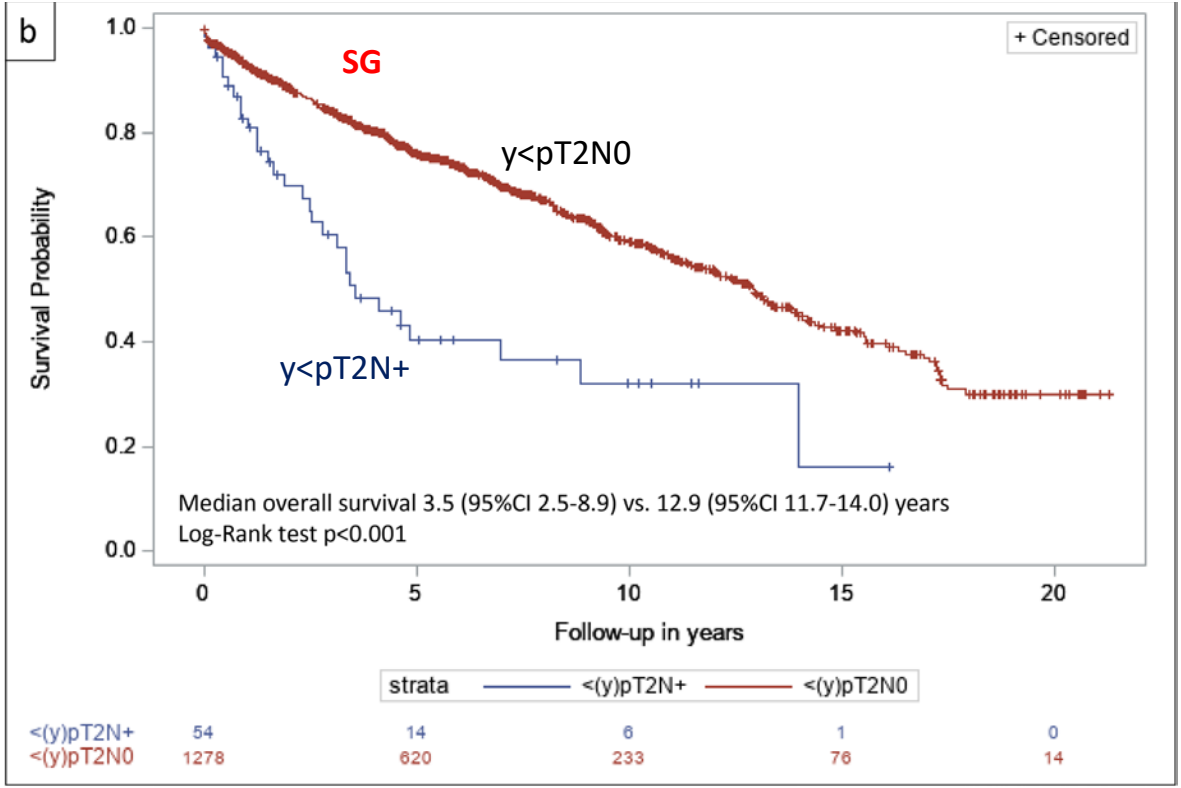
Patterns of recurrence after TMT



James et al, NEJM 2012

pN+ (ocultas) en RªC a QT / RT neoadyuvante

- Registro holandés CR (95-19); 1374 / 4657 (29.5%) con <ypT2
- **Incidencia pN+ en <(y)pT2, 4.3% (N = 59)**



Van Hoogstraten et al, World J Urol, Sep 2021

LDN en caso de Cistectomía parcial

Partial cystectomy:

Patient selection:

1. PC is not considered a standard option in MIBC, and this should be discussed with patients. PC can be discussed as an alternative to TMT or RC in very carefully selected patients with MIBC and small, solitary tumors amenable to resection with adequate margins that do not exhibit concomitant CIS or histologic subtype (excluding pure adenocarcinoma of the urachus) after adequate consultation about risks versus benefits of this approach.
2. PC should be offered to patients with urachal adenocarcinomas that are amenable for resection with adequate margins.
3. Prior to PC, random bladder or directed biopsies with blue light cystoscopy, if available, along with prostatic urethral biopsies should be considered to rule out concomitant CIS.

Technique:

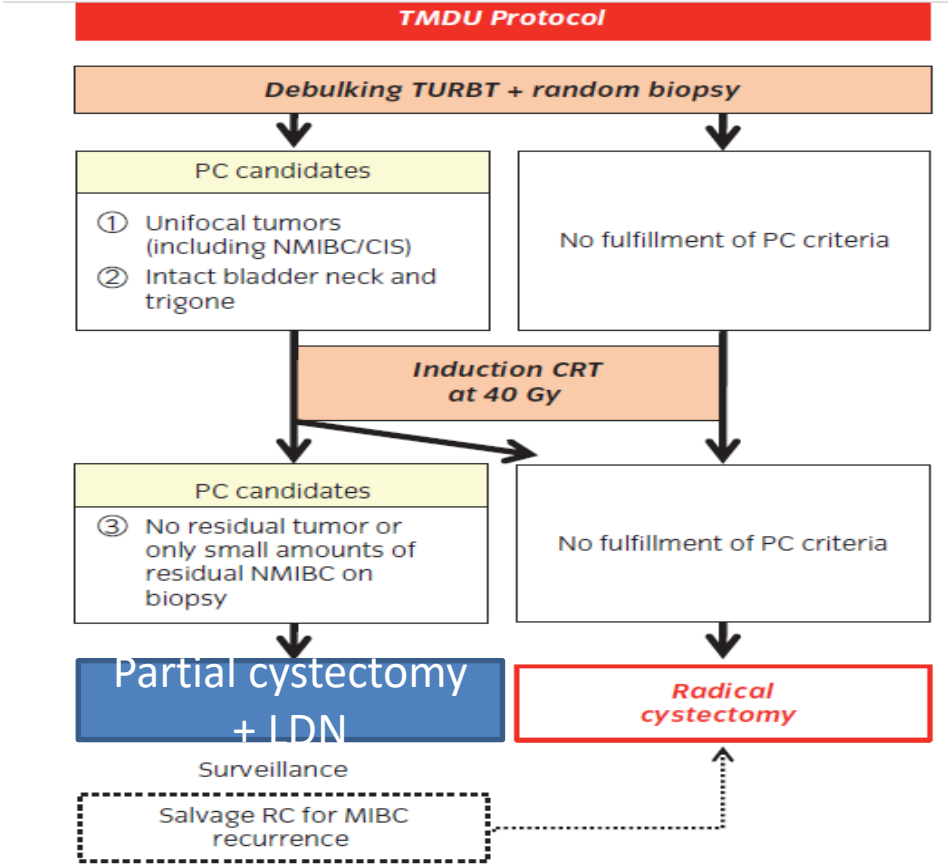
4. Cisplatin-based NAC should be offered to eligible patients with MIBC prior to PC. Risk-stratified adjuvant therapy should be offered based on PC pathology and available data.
5. Owing to the high rate of pathologic upstaging and frequent identification of squamous (variant) histology subtype of cT1 high-grade tumors in bladder diverticuli, fit patients with a high suspicion of more advanced-stage disease on imaging/examination and/or large volume in a bladder diverticulum should be offered cisplatin-based NAC prior to PC (a multidisciplinary review is important).
6. Standard bilateral pelvic lymphadenectomy should be performed in patients undergoing PC for MIBC.
7. Preventing intraoperative tumor and urine spillage during PC is critical to ensure optimal outcomes.

Follow-up and surveillance:

8. Follow-up after PC for MIBC should be patient-specific and include the following:
   (a) Cross-sectional imaging of the chest, abdomen, and pelvis every 3–6 mo for 2–3 yr, then at least annually for up to at least 5 yr.
   (b) Surveillance cystoscopy and urine cytology every 3–4 mo for the first 2 yr, then every 6–12 mo for up to 10 yr. Thereafter, lifelong annual cystoscopy should strongly be considered.

(Delphi IBCG) Gupta et al, Eur Urol 2025

Current Role of Partial Cystectomy + PLND in Bladder Preservation Protocols



- 1997-2010
- N=183 cT2-4a TMT

- 65 (36%) partial Cystectomy- only 3 (7%) had MIBC, all pN0
- No Recurrence or DOD

(Univ. Tokio) Koga et al, International Journal of Urology (2012) 19, 388–401

Manejo ganglios si empezamos 1º por Tratamiento sistémico: Neo-adyuvancia en cN_{1-3}

cN+; argumentos para CR+LDN de consolidación

A favor

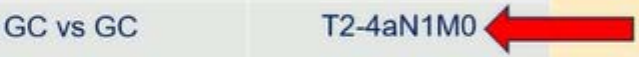
- La mayoría de EC de neoadyuvancia NO han incluido cN+
- A veces se objetiva progresión en ganglios con RC radiológica
- Eliminación de cáncer microscópico
- SG a 5 años de ypN+; 20%

En contra

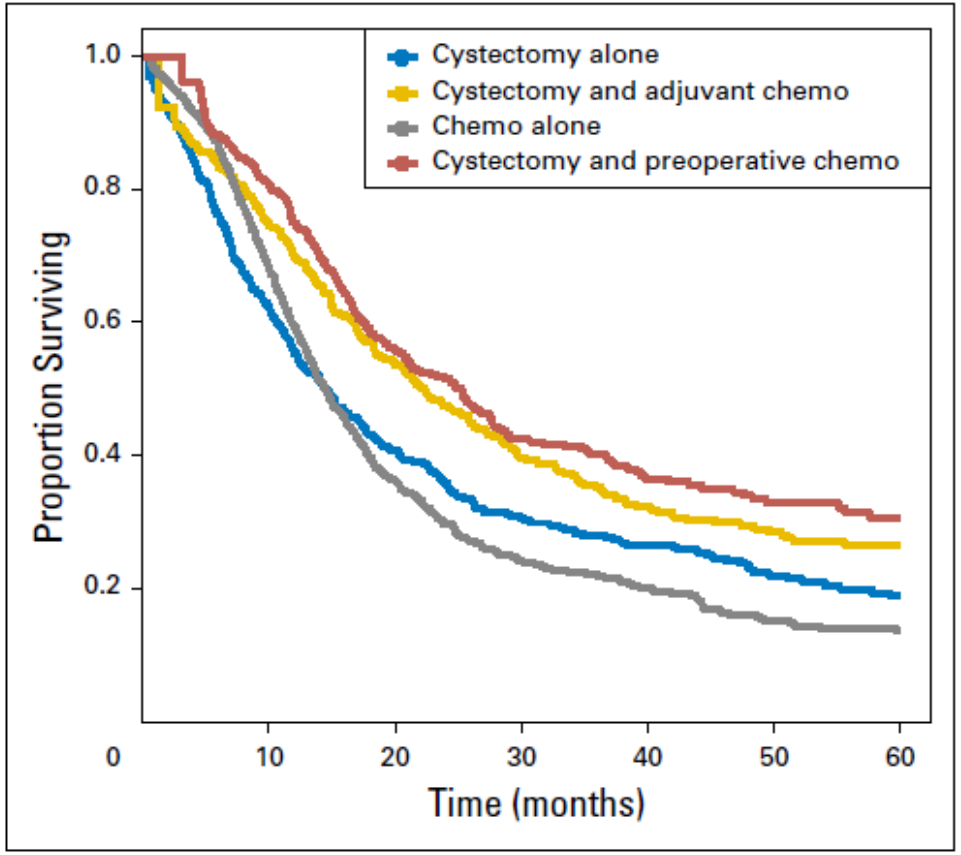
- Terapias sistémicas eficaces en RC/RP/EE (JAVELIN 100)
- El 50% de las RC de QT+IO (GemCIs + Nivo) se dan en cN+ (CHECMATE 901)
- En Pembro-EV (EV-302) HR 0.51 en cN+ y 50% respuesta duradera en respondedores

Fases III con IO; mayoría NO incluyen cN+

	Clinical Trial	N	Treatment Arms	Eligibility
CISPLATIN ELIGIBLE	KEYNOTE-866	870	Pembro + GC vs GC	T2-4aN0M0
	KEYNOTE-B15/EV-304	784	Pembro +EV vs GC	T2-T4aN0M0 T1-T4aN1M0
	NIAGARA	1050	Durva+ GC vs GC	T2-4aN1M0
	ENERGIZE	1200	Nivo + GC vs GC	T2-4aN0M0
CISPLATIN-INELIGIBLE	KEYNOTE-905/ EV-303	836	RC vs Pembro+EV vs Pembro	T2-4aN0M0
	VOLGA	830	RC vs Druva/Tremi+EV vs Durva+EV	T2-4aN0M0



4 estrategias en cT_x N_{1-3}

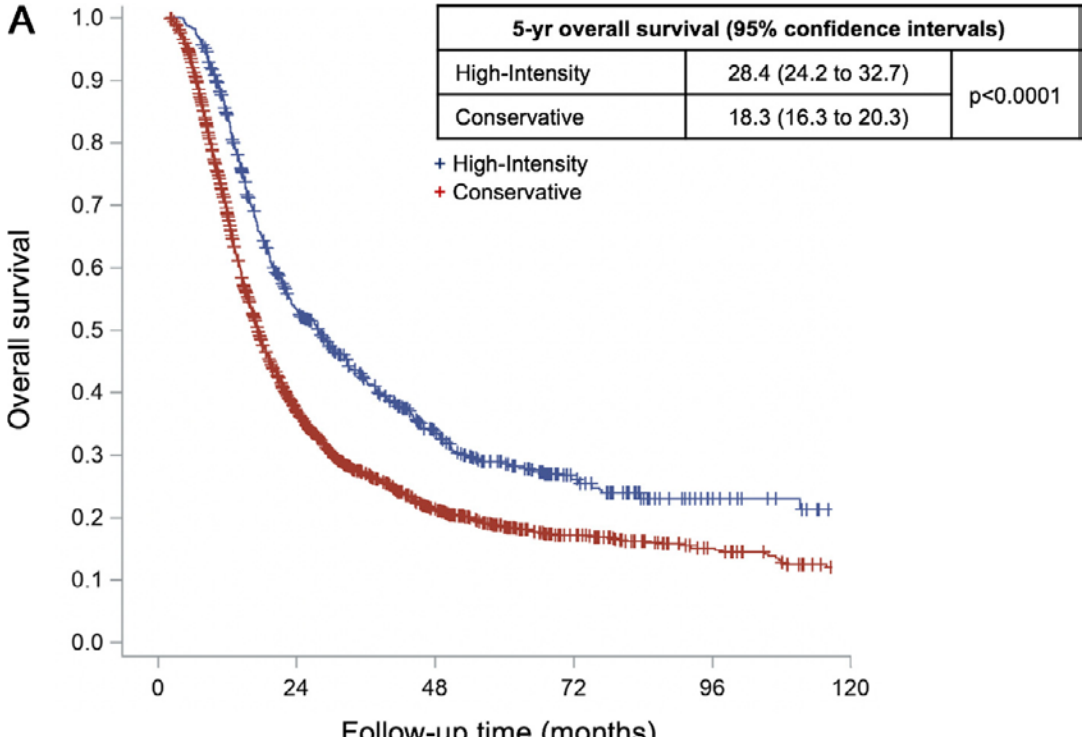


N=1739 pacientes
SG cruda a 5 años

- **QT terapéutica ; 14%**
- **CR; 19%**
- **QT neoadyuvante + CR; 31%**
- **CR + QT adyuvante; 26%**

(NCDB) Galsky et al J Clin Oncol 2016

$cTxN_{1-3}$; CR/RT+QT vs RTU+QT



+10% SG cruda
NNT = 9.9

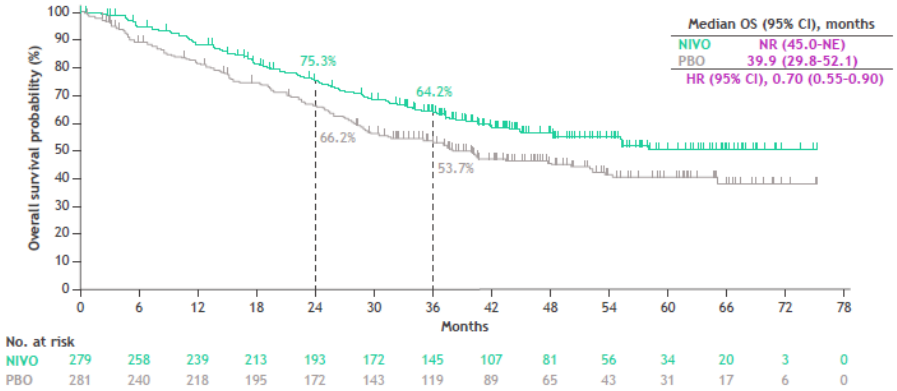
Multivariado;
- CCI 2
- cT4
- cN1 vs cN2-3
- Tto local vs NO

(NCDB) Sood et al , Urologic Oncology: Seminars and Original Investigations 2022

2025; ypN+ --- NIVO adyuvante

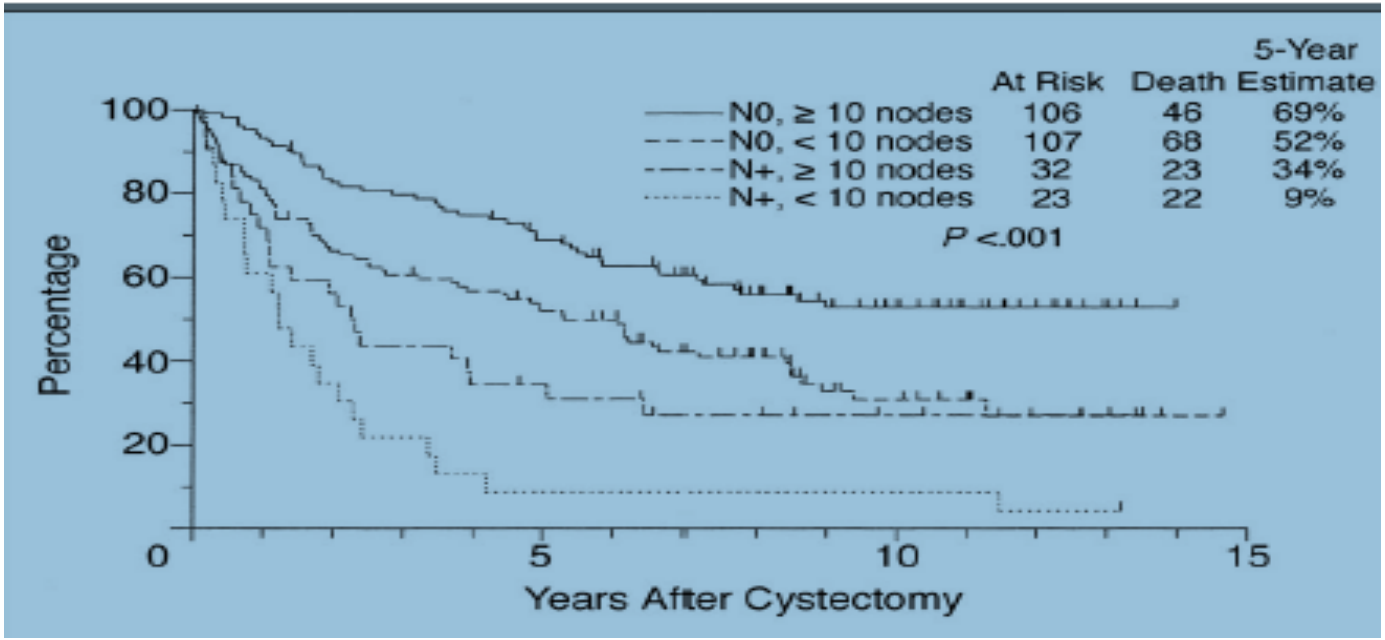
Characteristic	NIVO (n = 353)	PBO (n = 356)
Tumor PD-L1 ≥ 1% by IVRS, %	39.7	39.9
Prior neoadjuvant cisplatin, %	43.3	43.5
Pathologic T stage at resection,[c] %		
pT0–2	22.7	24.2
pT3	58.4	57.3
pT4a	16.1	17.4
pTX	1.4	0
pTis	1.1	0.8
Nodal status at resection,[c] %		
N+	47.3	47.2
N0/x with < 10 nodes removed	26.6	27.8
N0 with ≥ 10 nodes removed	25.8	24.7

OS[a]: all randomized patients with MIBC



(CHECMATE 274) Bajorin et al, NEJM 2021

NeoAdyuvancia; influencia en resultados de la calidad de la CR

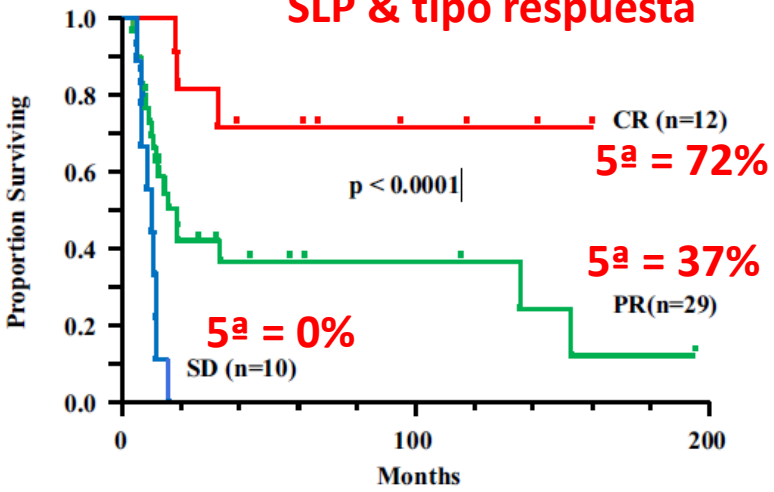


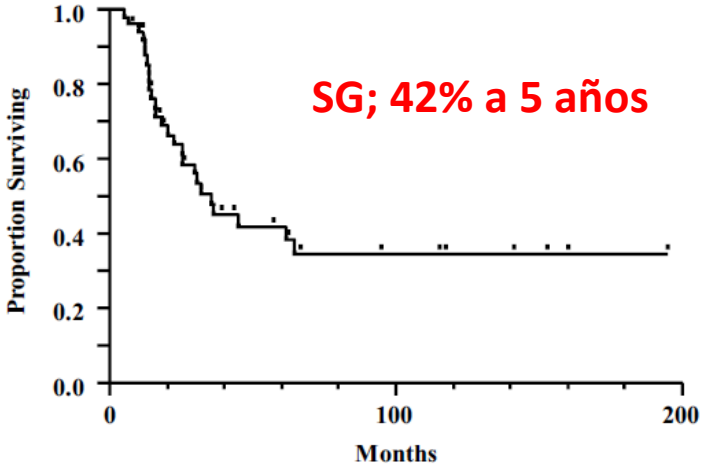
(MSKCC) Herr et al , JCO, 2004; 22:2781-2789

Respuesta tras NeoAdyuvancia en cN+; influencia de la CR en supervivencia

60 TCC cN+ tras QT (-9 EP) = 51 ptes con Cirugía+LDN de consolidación

SLP & tipo respuesta

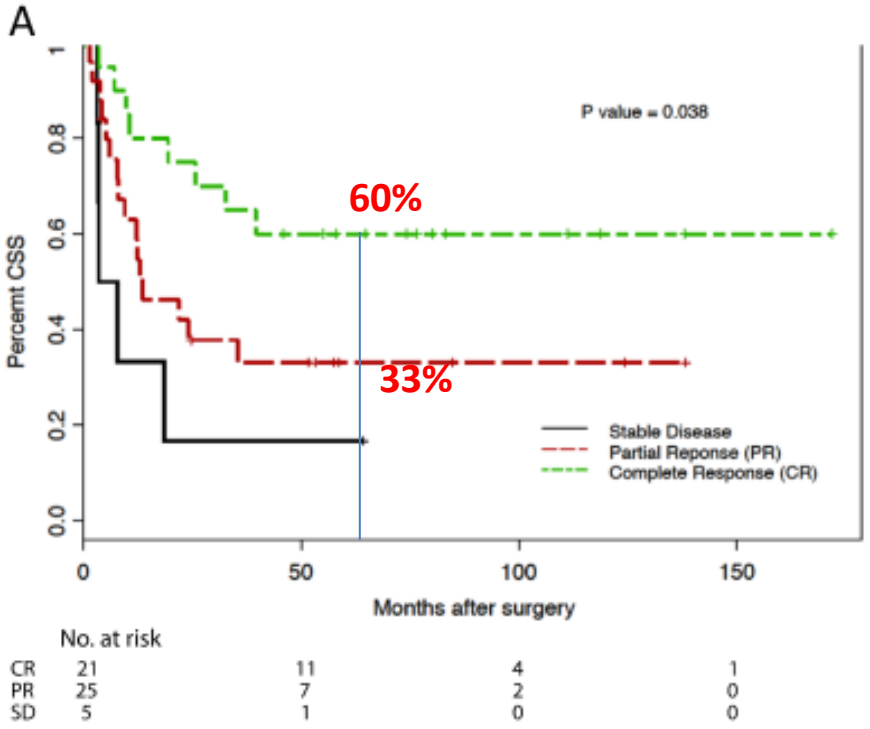


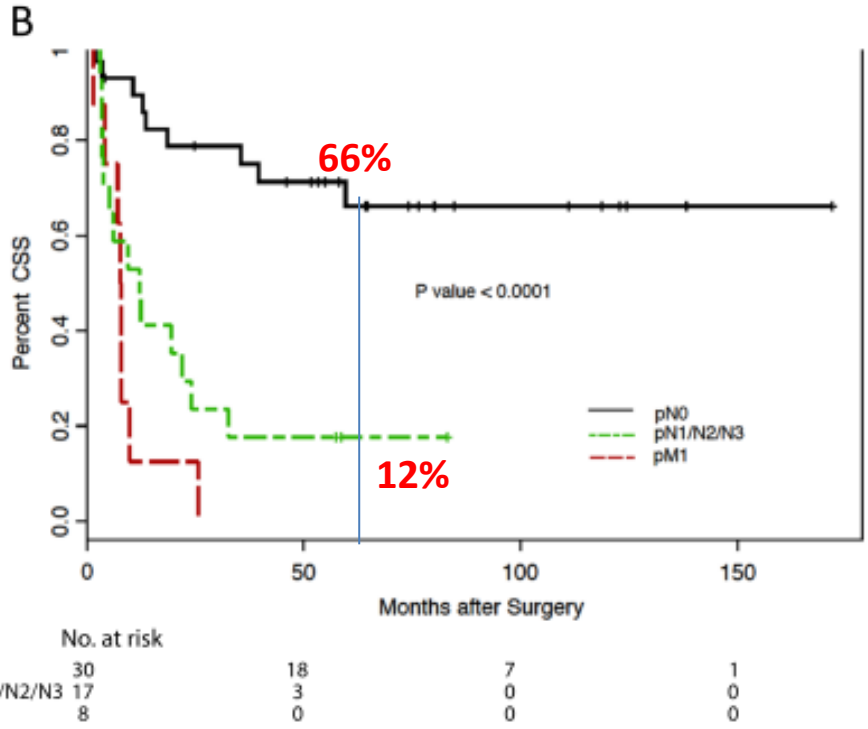


(Ins. Nac. Cáncer JAPON) Urakami et al, Int J Clin Oncol 2015; 20:1171–1178

“NeoAdyuvancia” en cT_x N_{1-3}

N=55 ptes

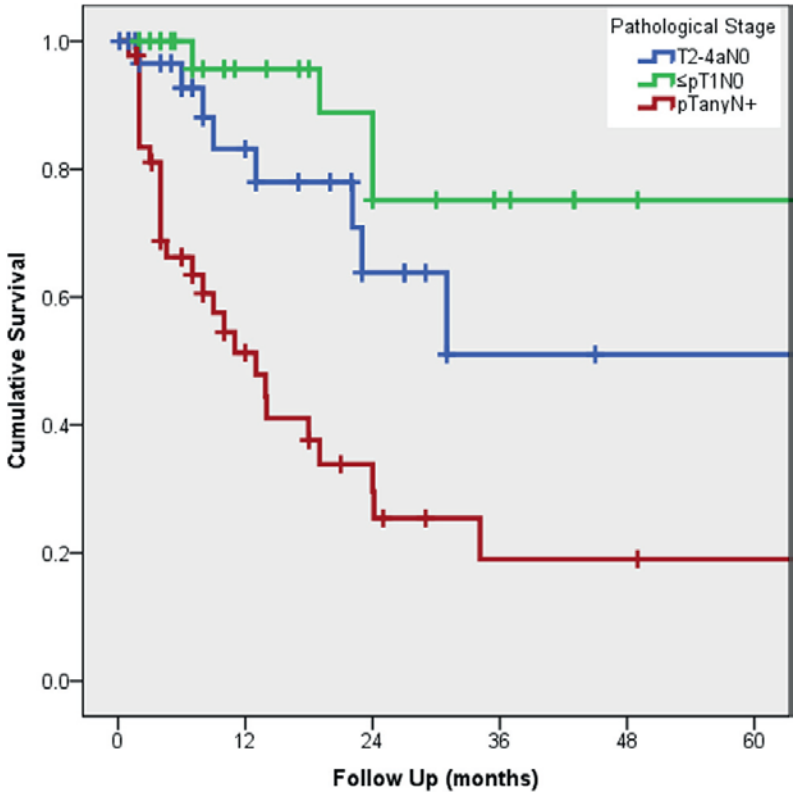




… pero 26% of patients with radiologic CR had pN+

(MD Anderson) Ho et al, Urologic Oncology: Seminars and Original Investigations 2016; 34

“NeoAdyuvancia” en cT_x N_{1-3}



N=304 pacientes

- **48% de cN1-3 --- pN0**
- **24% fueron pT0**
- **38% de los pT0 post QT ---- pN+**
- *****Respuesta completa global; solo 14.5%**

MVA para SG;

- **pN0**
- **Nºgg extraídos > 15**
- **R0**
- **Haber llevado CISplatino**

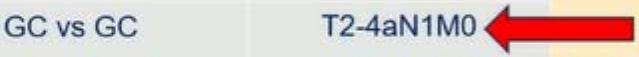
(no diferencias cN1 vs cN2-3)

(Multicéntrico) Zargar et al J Urol 2016; 195: 53-59

Nuevas líneas ante cN+

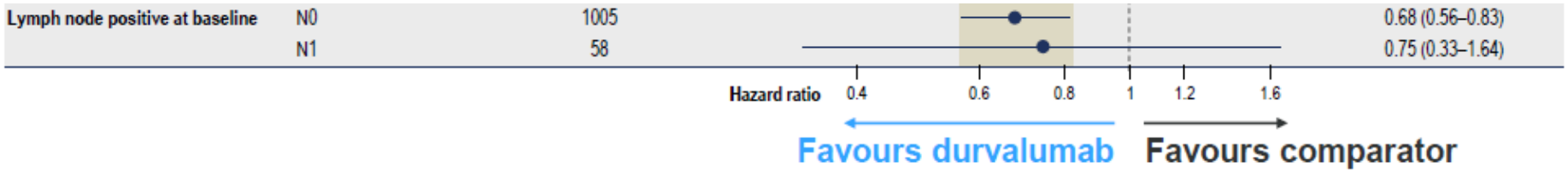
Fases III con IO; mayoría NO incluyen cN+

	Clinical Trial	N	Treatment Arms	Eligibility
CISPLATIN ELIGIBLE	KEYNOTE-866	870	Pembro + GC vs GC	T2-4aN0M0
	KEYNOTE-B15/EV-304	784	Pembro +EV vs GC	T2-T4aN0M0 T1-T4aN1M0
	NIAGARA	1050	Durva+ GC vs GC	T2-4aN1M0
	ENERGIZE	1200	Nivo + GC vs GC	T2-4aN0M0
CISPLATIN-INELIGIBLE	KEYNOTE-905/ EV-303	836	RC vs Pembro+EV vs Pembro	T2-4aN0M0
	VOLGA	830	RC vs Druva/Tremi+EV vs Durva+EV	T2-4aN0M0

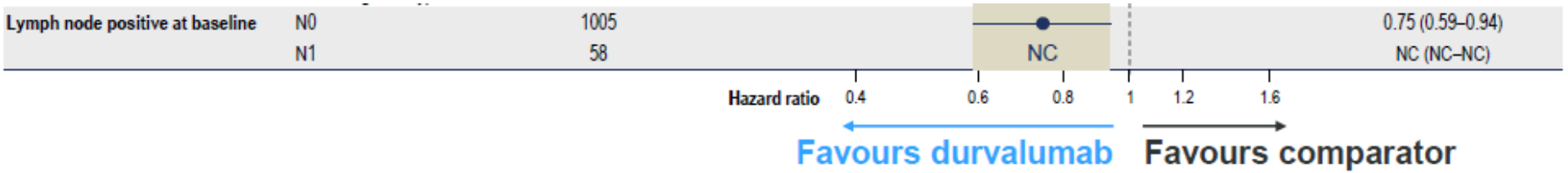


DURVA + GEM/CIS + DURVA adyuvante vs GEM/CIS

NIAGARA: Event-free Survival Subgroup Analyses



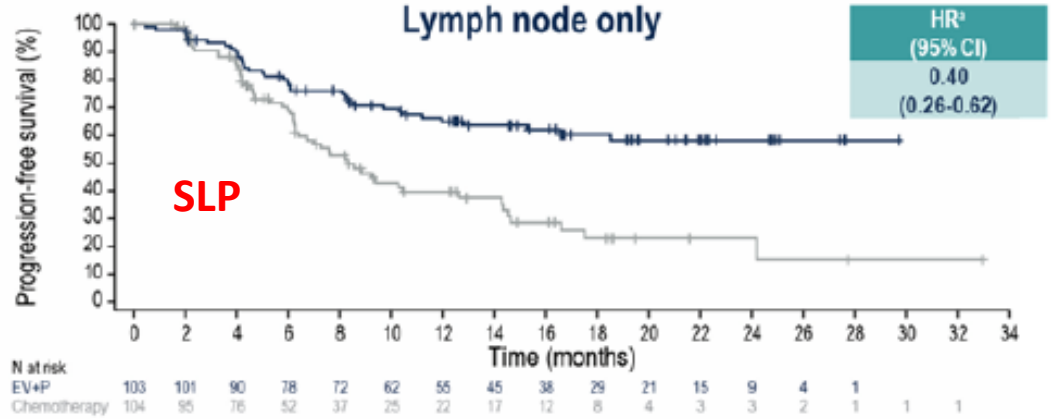
NIAGARA: Overall Survival Subgroup Analyses

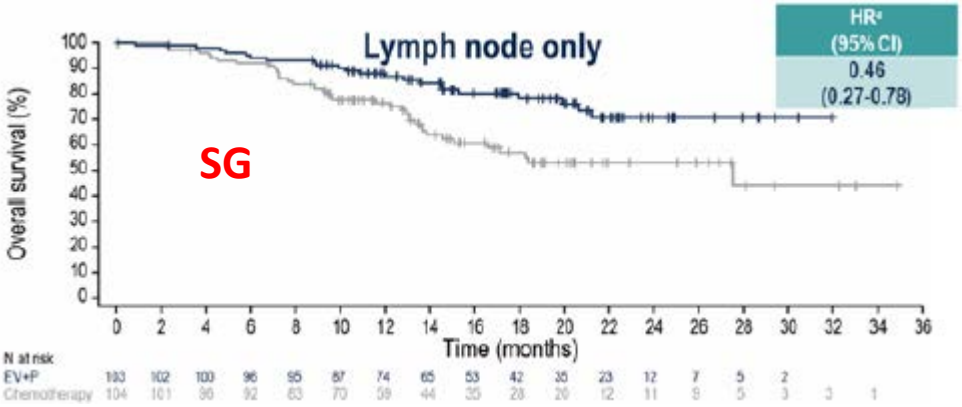


(NIAGARA) Powles et al, NEJM 2024

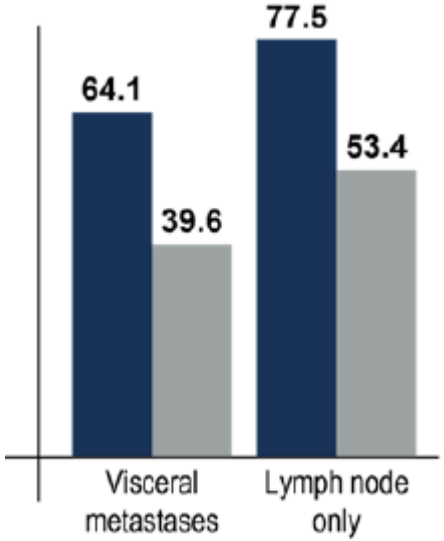
EV-302 ; EV+Pembro vs QT; comportamiento en cN+

Enfemedad solo ganglionar; 23%



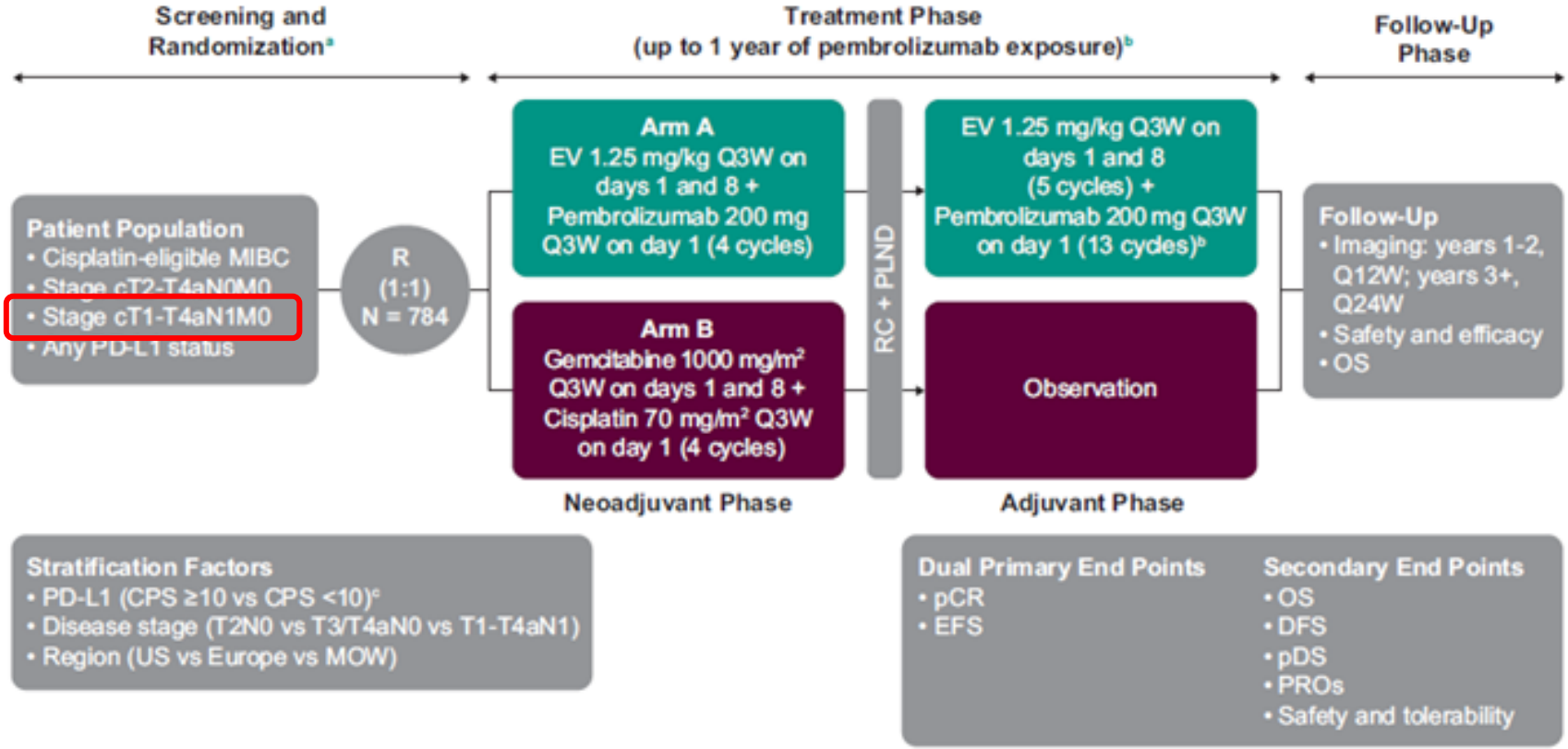


Tasa de respuesta objetiva



Van der Heijden et al, ESMO 2024

Pembro +/- EV neo + adyuvantes



CONCLUSIONES

- Los datos presentados del rol de la Cirugía tras respuesta completa o parcial vienen de la era de la QT basada en platinos y la mayoría sin incluir cN+
- Habrá que valorarlos en el contexto de nuevas armas terapéuticas como la INMUNOTERAPIA Y LOS ANTICUERPOS CONJUGADOS por los datos de NIAGARA, JAVELIN, CHECKMATE 901 y EV-Pembro 302 (y a la espera del resto de EC con tto combinado peroperatorio)
- Necesidad de un mejor estadiaje pre-tratamiento y post-tratamiento
- Potencial rol (también) del ctDNA y utDNA en el futuro para guiar a qué pacientes cistectomizar
- De momento; el rescate quirúrgico de cN+ es recomendable en RESPUESTAS COMPLETAS radiológicas y ha de INCLUIR LA LDN