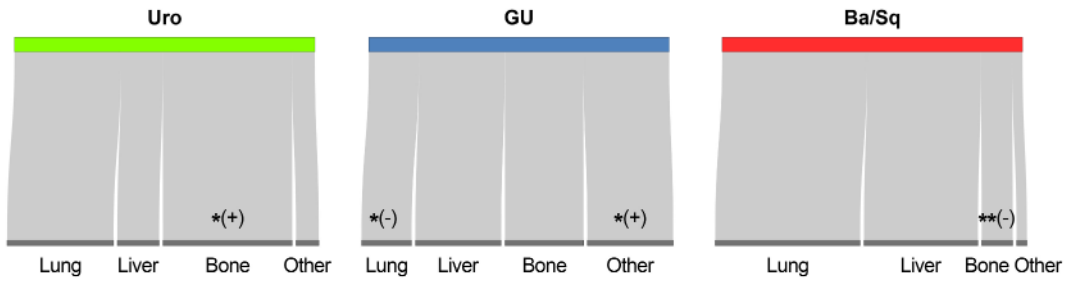
# Heterogeneidad tumoral en análisis de muestras pareadas de carcinoma urotelial primario y metástasis en tejido de autopsia.

Marta Sotelo García. Becas GO NORTE 2023

# Motivación

- Localización del tumor primario, histología y subtipo molecular → patrón metastásico.
  - Heterogeneidad tumoral y selección clonal serán mecanismos de resistencia terapéutica.
  - El patrón de metástasis puede reflejar afinidad tumoral por microambientes específicos.




Sjödahl et al *IJC* 2023

**Diferencias en respuesta terapéutica y resultados de supervivencia basados en localizaciones metastásicas destacan el impacto del patrón de diseminación en la eficacia de la terapia sistémica.**

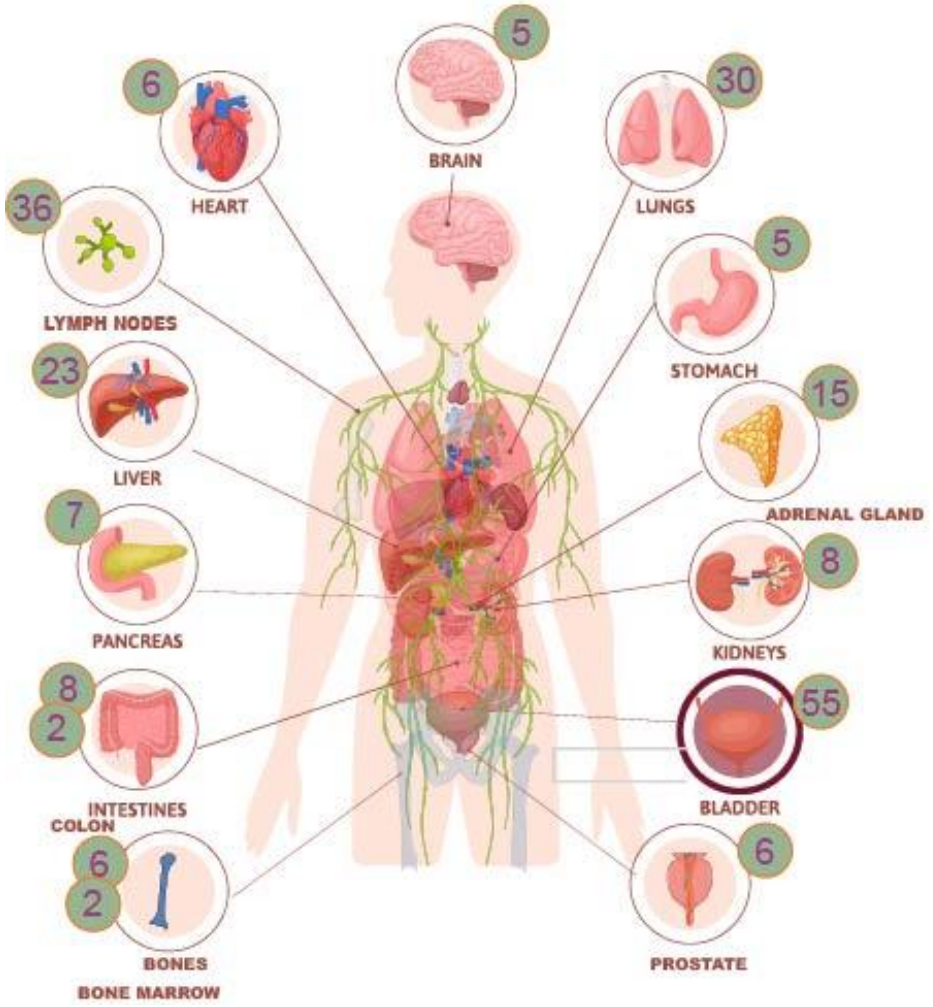
# Caracterización integral del cáncer de vejiga a través de autopsias

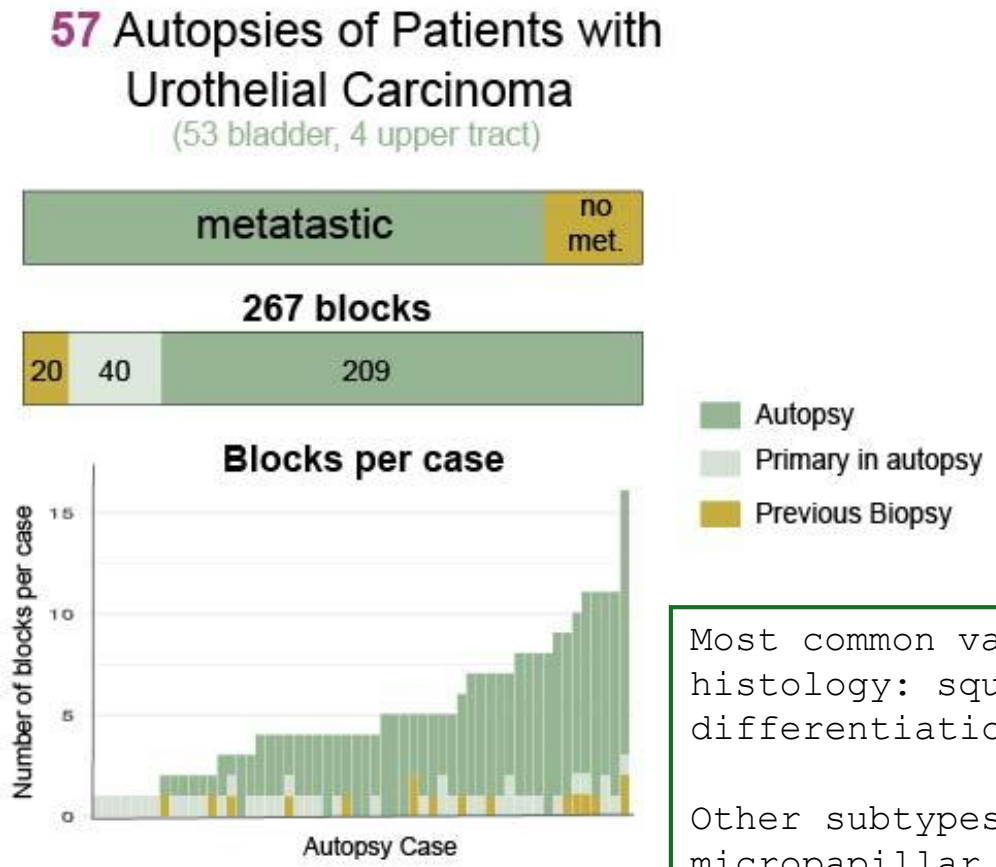
- Muestras de primario y todas las localizaciones metastásicas.
- Obtención de biopsias pre-tratamiento.
- Detectar micrometástasis y su subtipo.

# Objetivos

- Estudio histológico de la heterogeneidad de subtipos tumorales CU en lesiones metastásicas de un mismo paciente.
- Caracterización inmunohistoquímica y realización de análisis genómico.
- Correlación de hallazgos con la enfermedad, uso de tratamientos y respuesta obtenida.

# The cohort



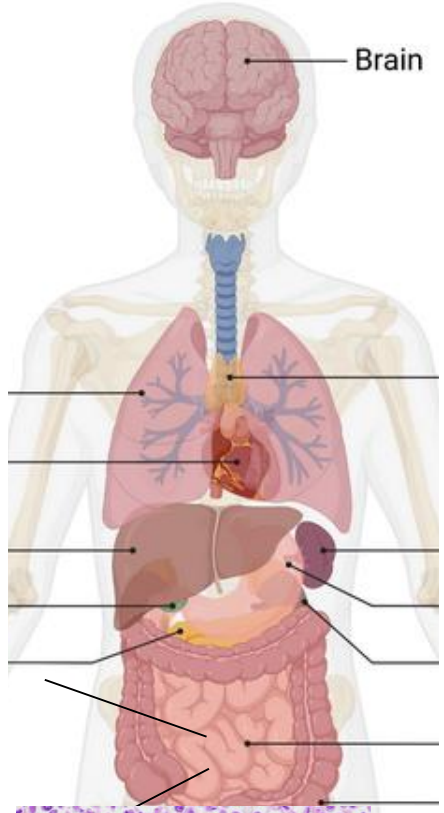

Most common variant histology: squamous differentiation.

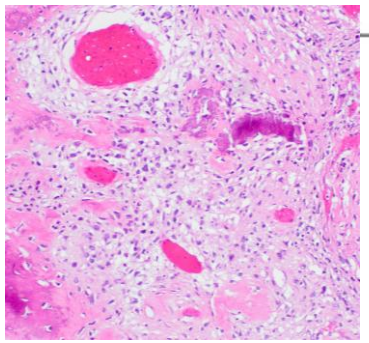
Other subtypes: plasmacitoid, micropapillar, sarcomatoid.

Divergent histological subtype Primary-Mets: 15%.

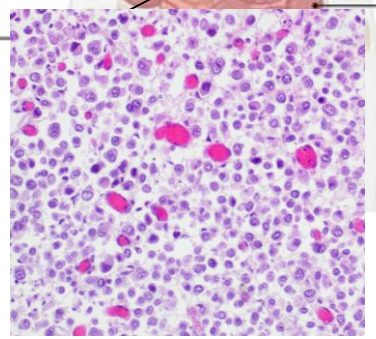
Marques M, Azueta A, et al. 2025

# Bladder Cancer with Urothelial Carcinoma Plasmacytoid and Sarcomatoid Variants



**BLADDER**
Sarcomatoid

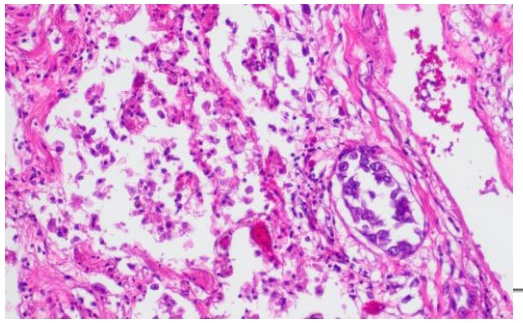


**BLADDER**
Urothelial ca.
plasmacitoid variant

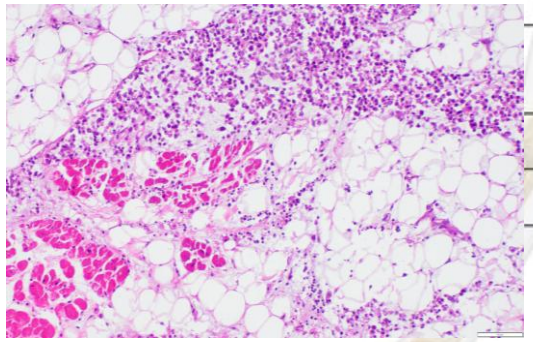
Azueta A, et al. 2025

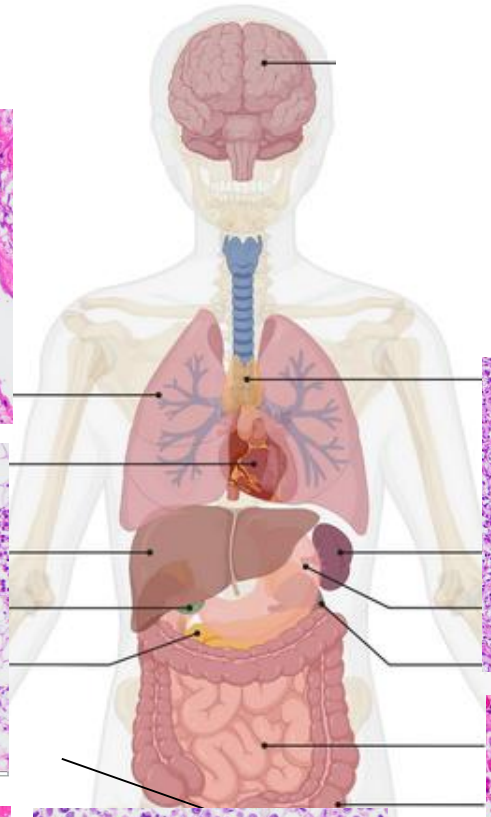
**Intratumor heterogeneity**
**Early clone metastasis**
**Metastatic site adaptation**

**LUNG**
Urothelial ca.

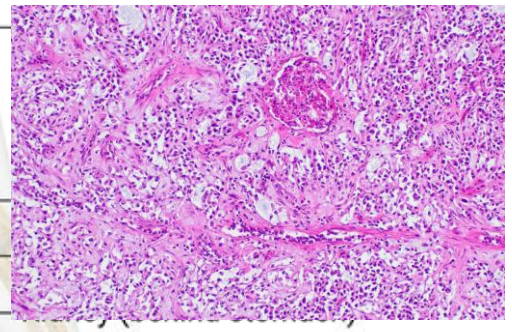


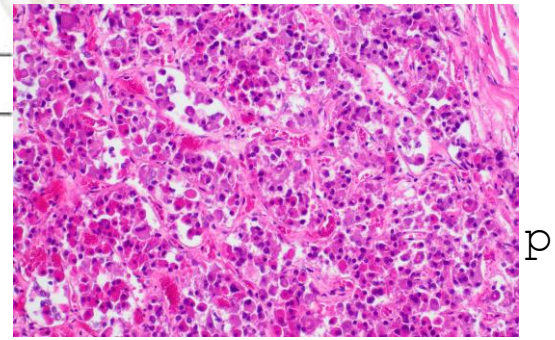
**HEART**
Urothelial ca.



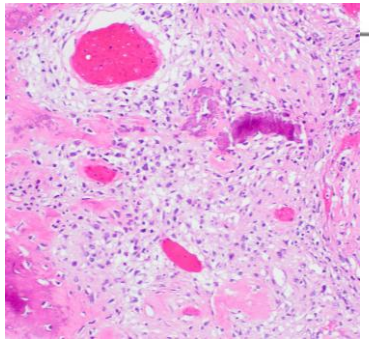


**KIDNEY**
Urotelial ca.

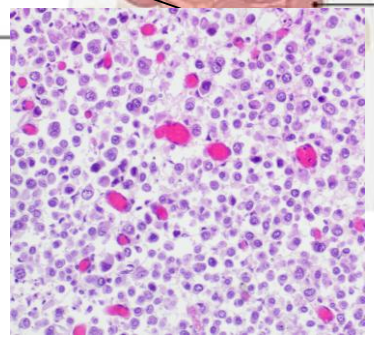




**LYMPH NODE**
Urothelial ca, plasmacitoid-rhabdoid subtype



**BLADDER**
Sarcomatoid

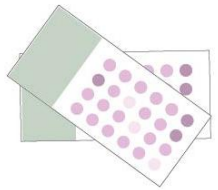


**BLADDER**
Urothelial ca., plasmacitoid variant

Azueta A, et al. 2025

## 267 blocks

Histopathology review



Construct tissue microarrays

DNA extraction

RNA extraction

**Histologic Variants**

**IHC markers**

Urothelial differentiation
Therapeutic/predictive antigens
Histologic subtype
Tumor microenvironment
Proliferation
epithelial–mesenchymal transition

**sWGS (4x)**

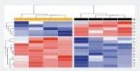
**CNVAs**

**Phylogenetic Inference**

clones & timing

**3′ RNA-seq**

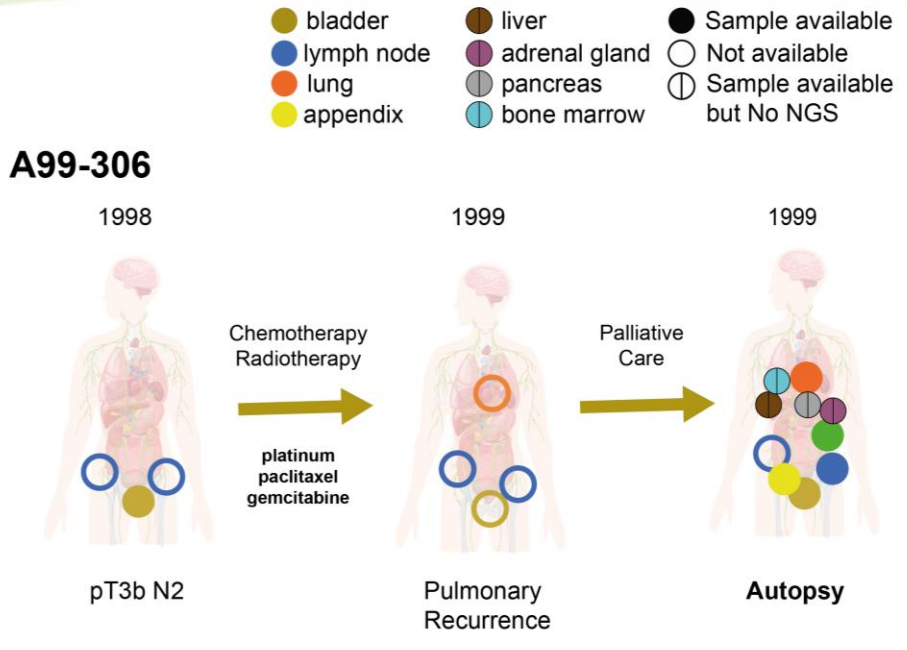
**gene-expression**

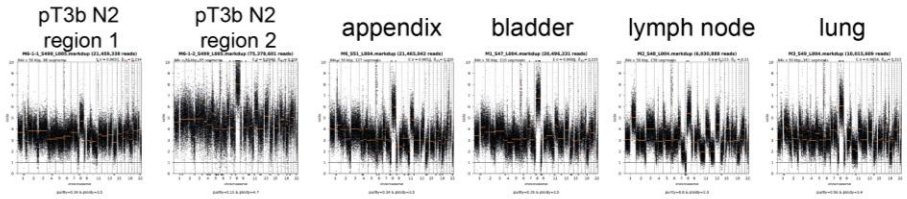


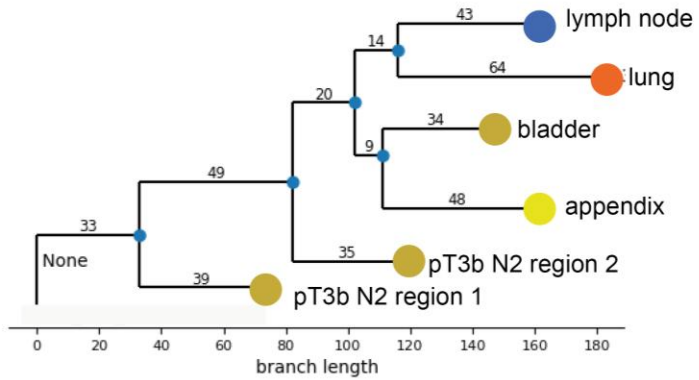
assign molecular subtypes

## Integrate with Clinical Story

Infer route & evolution of disease




Metastatic clones arise from a specific region of primary tumor

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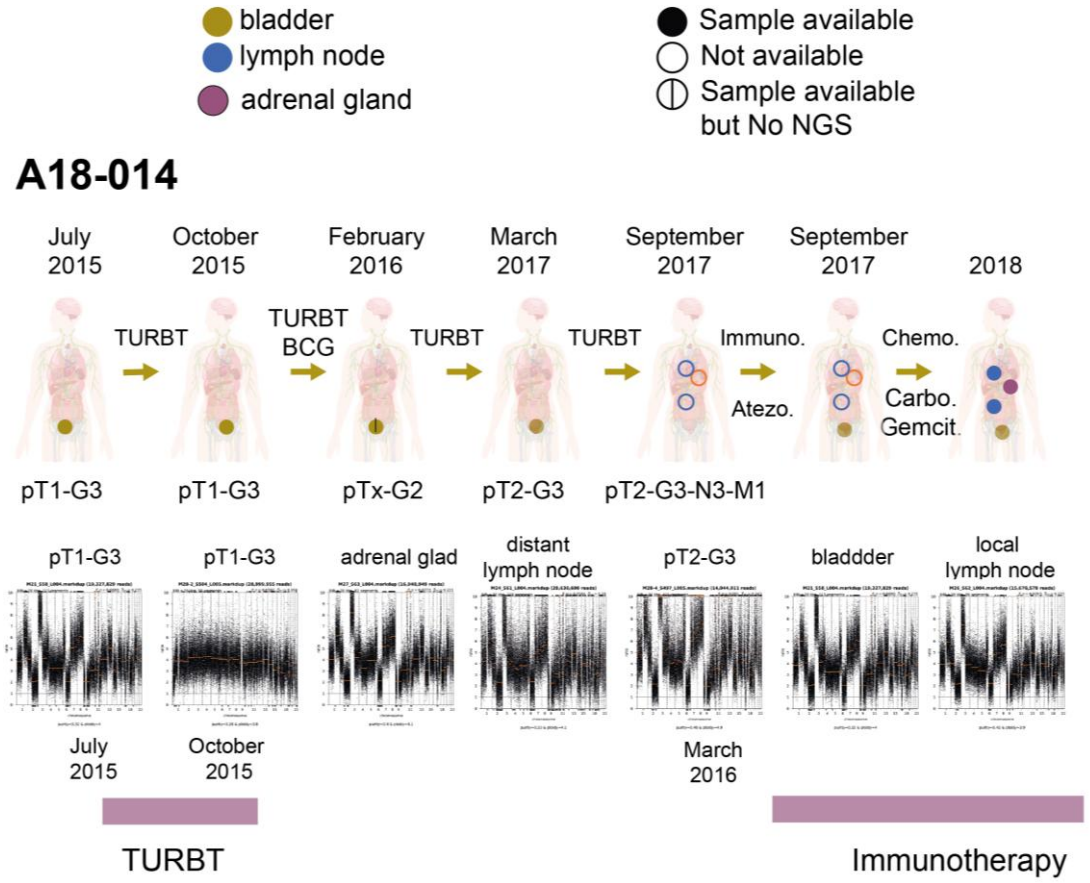
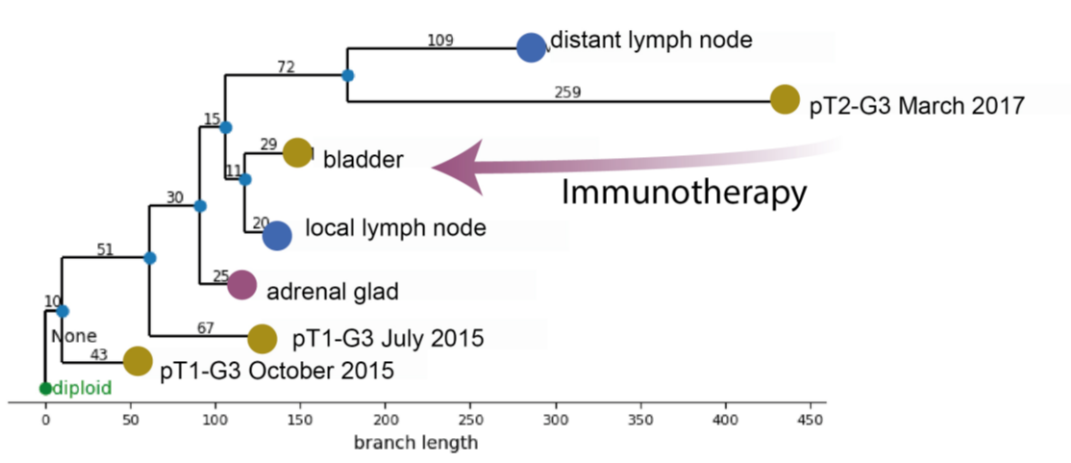



Tumors can spread within the same patient through distinct lymphatic routes and metastasize to distant organs via hematogenous pathways at the same time

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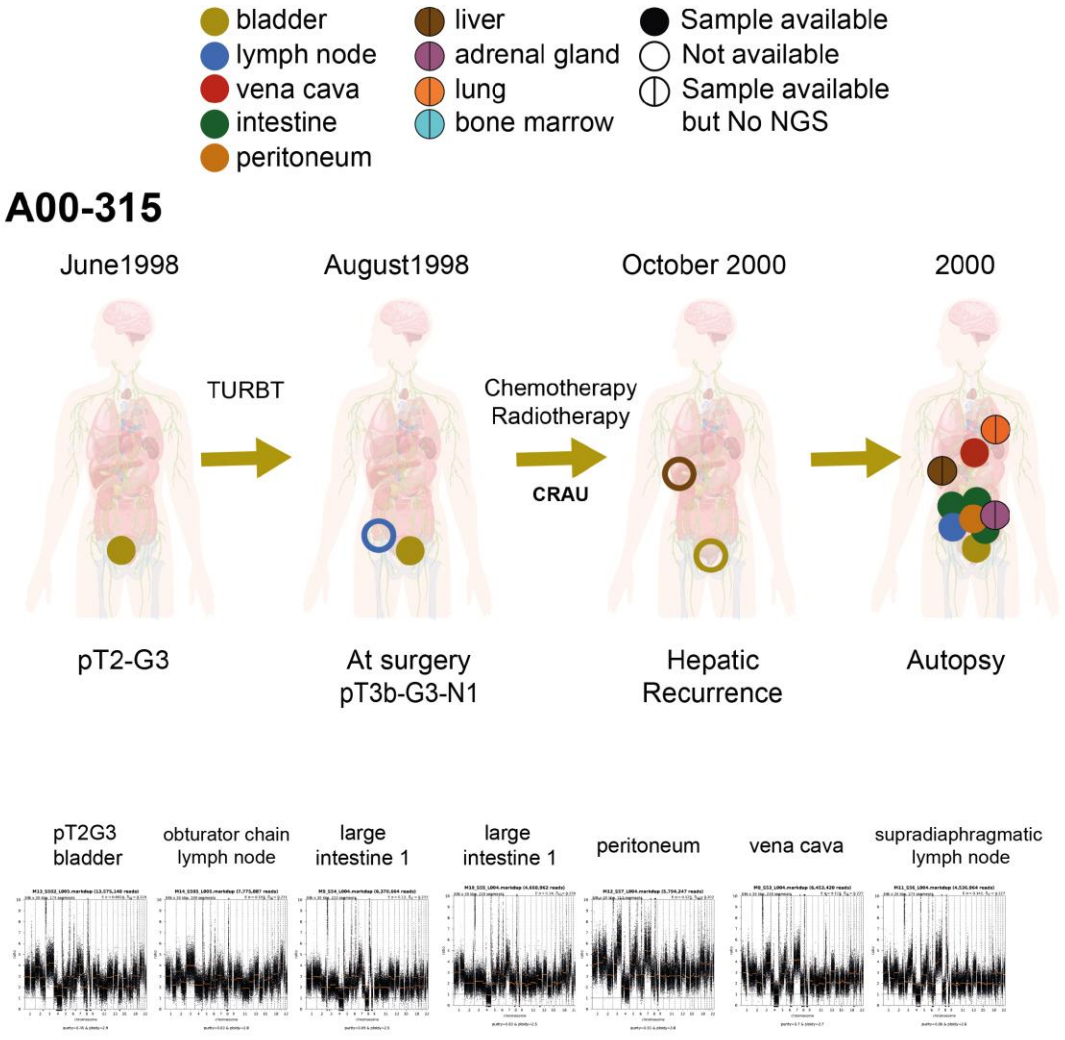
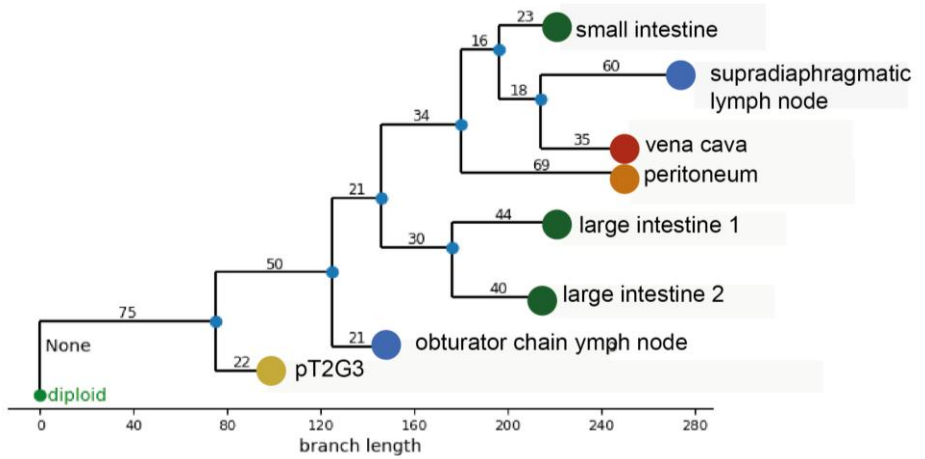



Metastases in lymph nodes and distant organs originated from an early clone preceding the T2 biopsy.

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# Preliminary Results

- Retrospective paraffin-embedded material from autopsies can be used for genomic analysis.

- There is no direct correlation between spatial and evolutionary distances.

- Lymphatic and hematogenous dissemination occur in parallel rather than sequentially.

- The more differentiated histology and less evolved genomic profiles of some distant metastases suggest early clone metastatic seeding. Genomic biomarkers of metastasis may be detectable in TURB, cystectomy, and lymphadenectomy biopsies.

- Genetic and transcriptomic evolution show partial but imperfect correlation


**Tumor purity** should be assessed in all samples to rule out normal tissue contamination and ensure accurate evolutionary and transcriptomic analyses. These conclusions may be influenced by **tissue conditions and should be validated in prospective cohorts.**

# CONCLUSSIONS

- Heterogeneous disease can influence different site responses.
- Despite initial morphology, cells at diagnosis may already present highly unstable genomic profiles.
- Oncological diagnosis and treatment must take care of UC as a time-changing disease for comprehensive approach.

# ¡Muchas gracias!