

# HER2 expression in primary bladder tumors and paired regional lymph nodes: relationship to cell cycle profile

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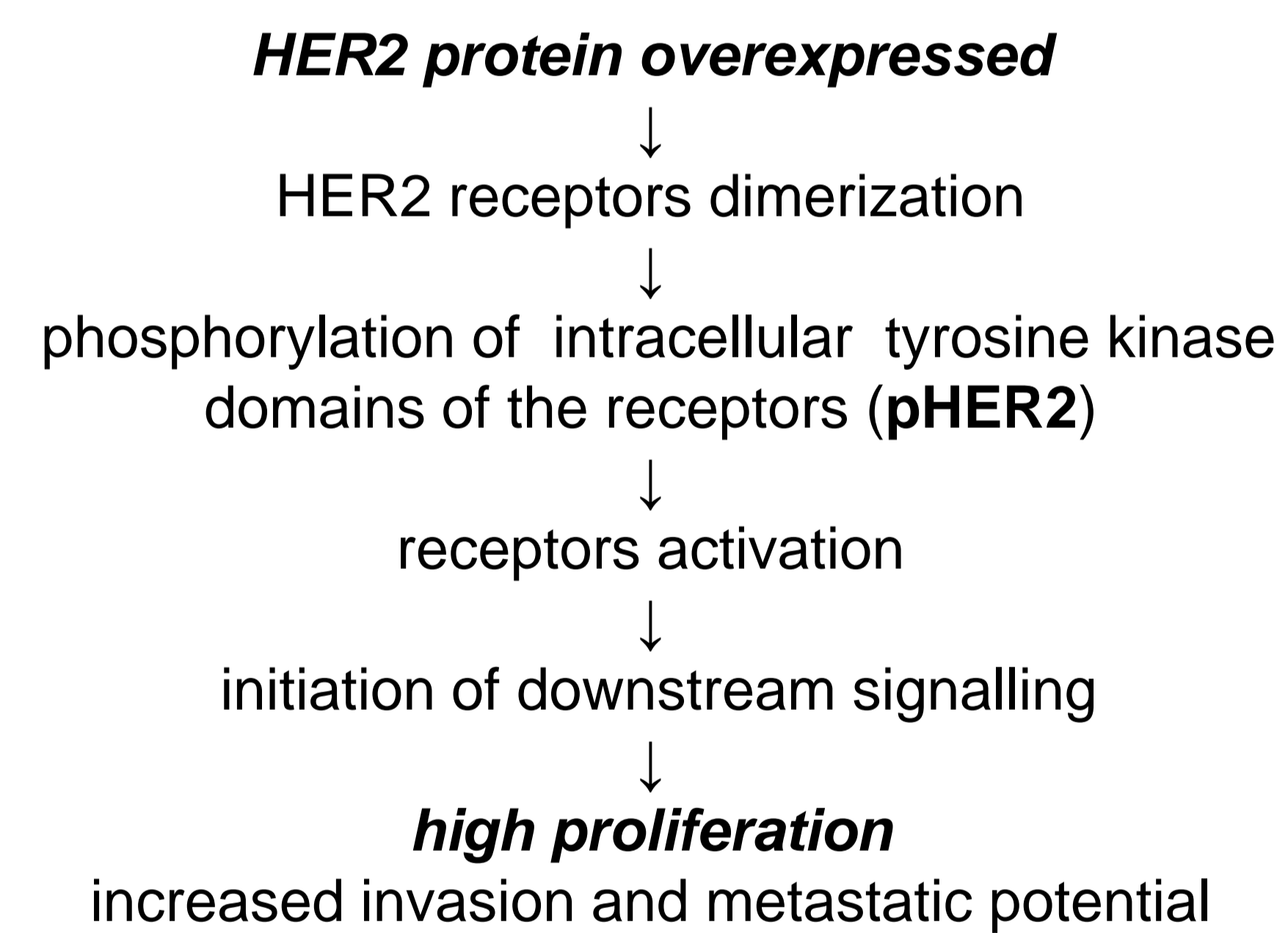
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## Background

Human epidermal growth factor receptor 2 (HER2) plays an important role in the aberrant proliferation of cancer cell with modification of cell cycle profile. Phosphorylation of specific tyrosine residues in the intracellular domains of the HER2 receptor leads at the functional and active form of HER2 (pHER2) and also is a precondition for downstream signalling network involved in cell growth, invasion and metastasis.

The proliferative activity and the invasive potential of tumors reflected by the percentage of cells involved in different phases of the cell cycle can be evaluated by cell cycle profile analysis.

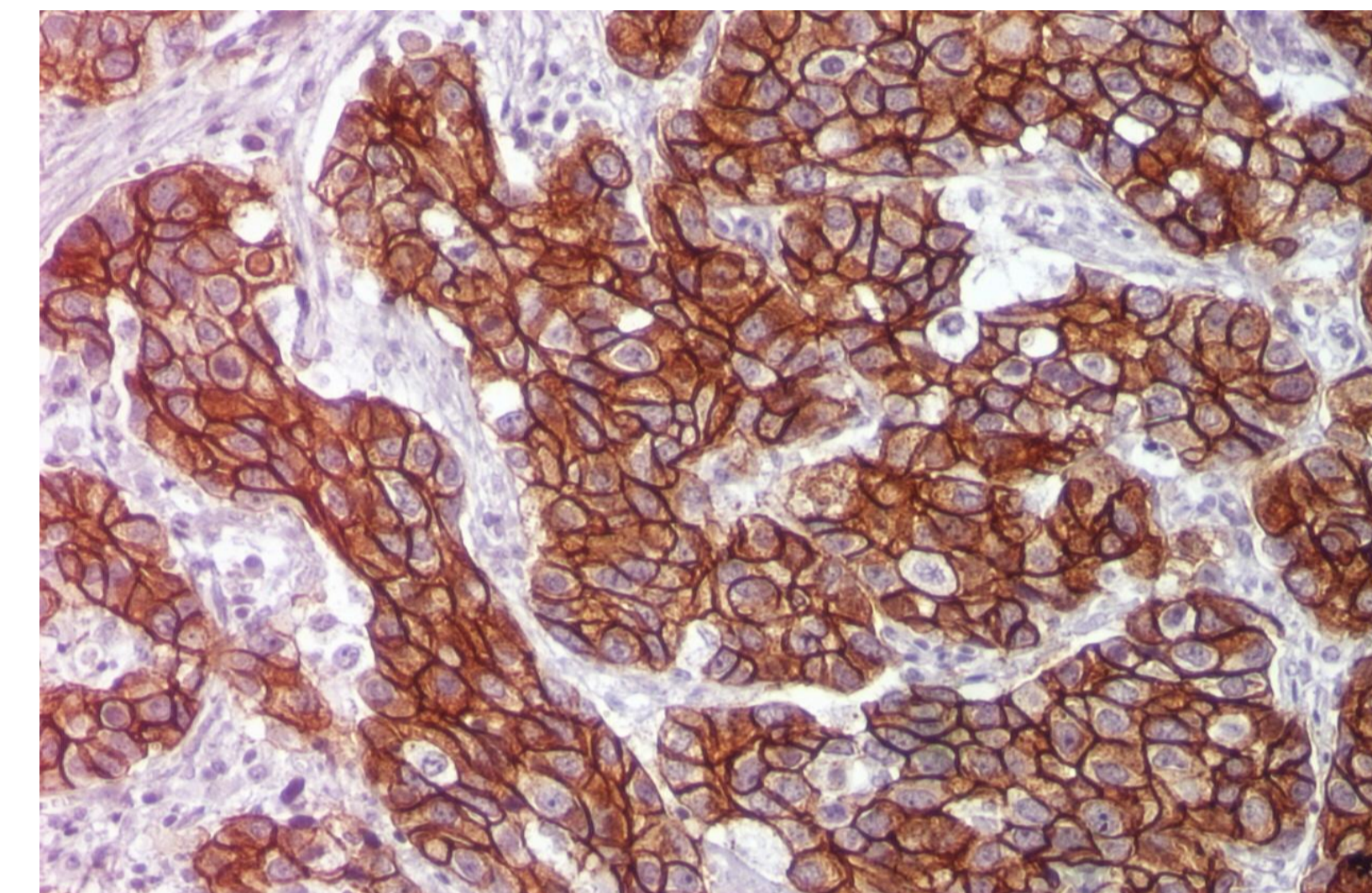
The aim of our study was to investigate the HER2 protein expression in both primary tumors and paired regional lymph nodes in relation to cell cycle profile in bladder cancer.



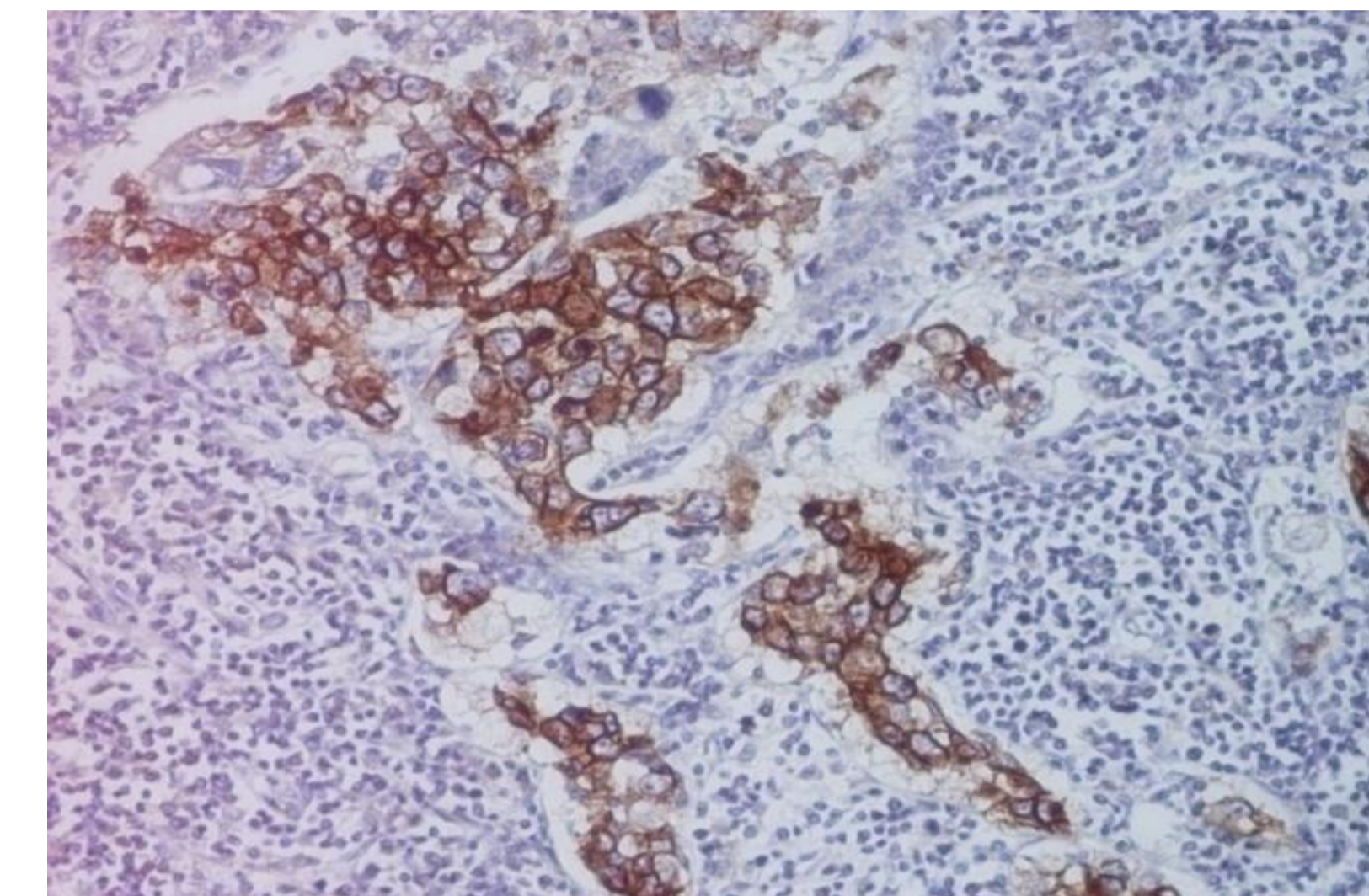
## Methods

- primary tumors and corresponding regional lymph nodes samples were obtained from 21 patients with bladder cancer and a mean age 62 years (range 41 to 78).
- 12 cases had regional lymph node metastases and 9 cases were without regional lymph node metastases.
- formalin-fixed, paraffin-embedded sections of bladder carcinomas and regional lymph nodes were immunohistochemical stained for HER2 expression.
- primary tumors were also investigated by immunohistochemistry for pHER2 and by flow cytometry for cell cycle profile.
- DNA content from a single cell suspensions (freshly frozen tissue) was analyzed by flow cytometry for cell cycle phases.

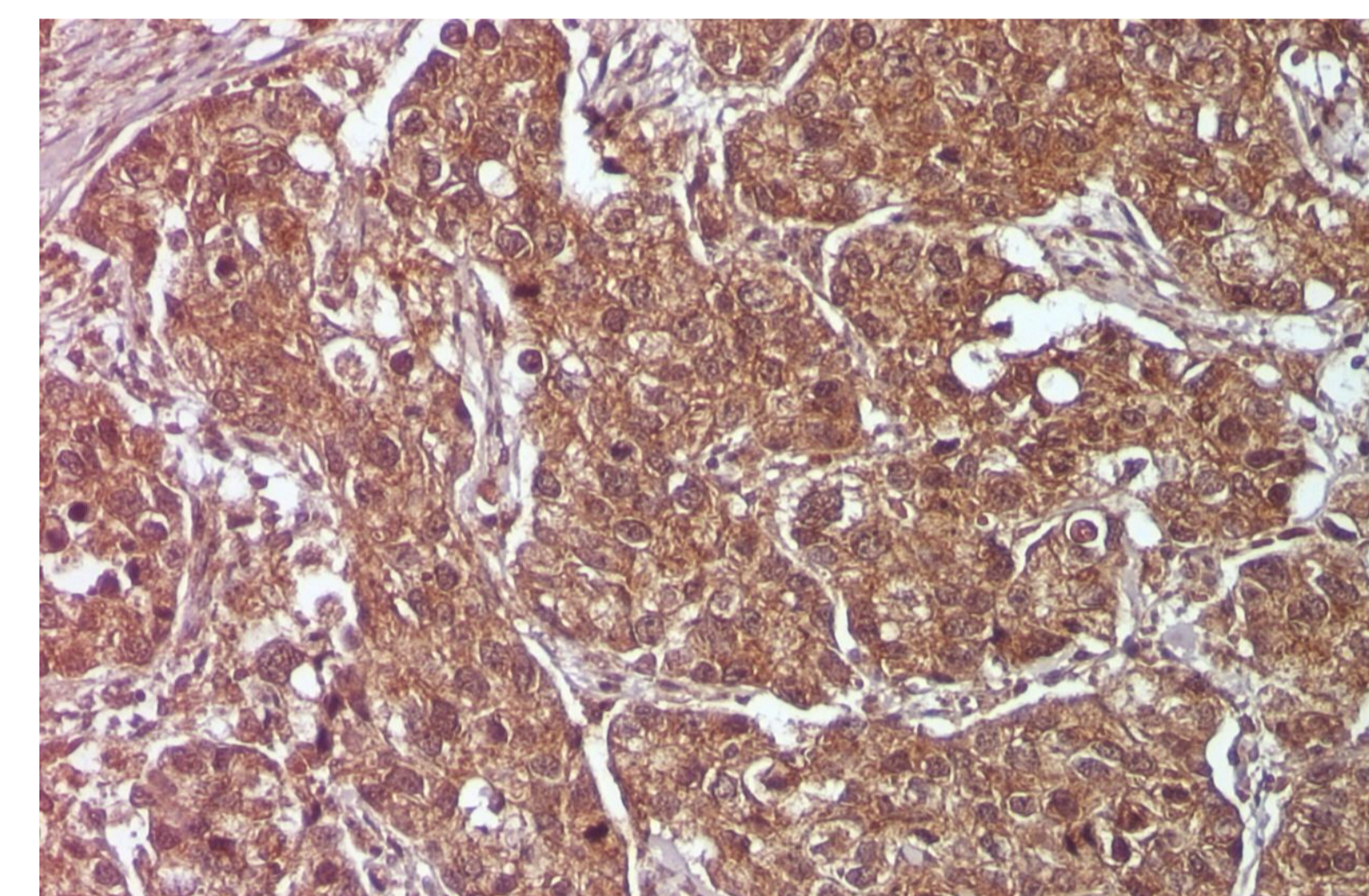
## Results



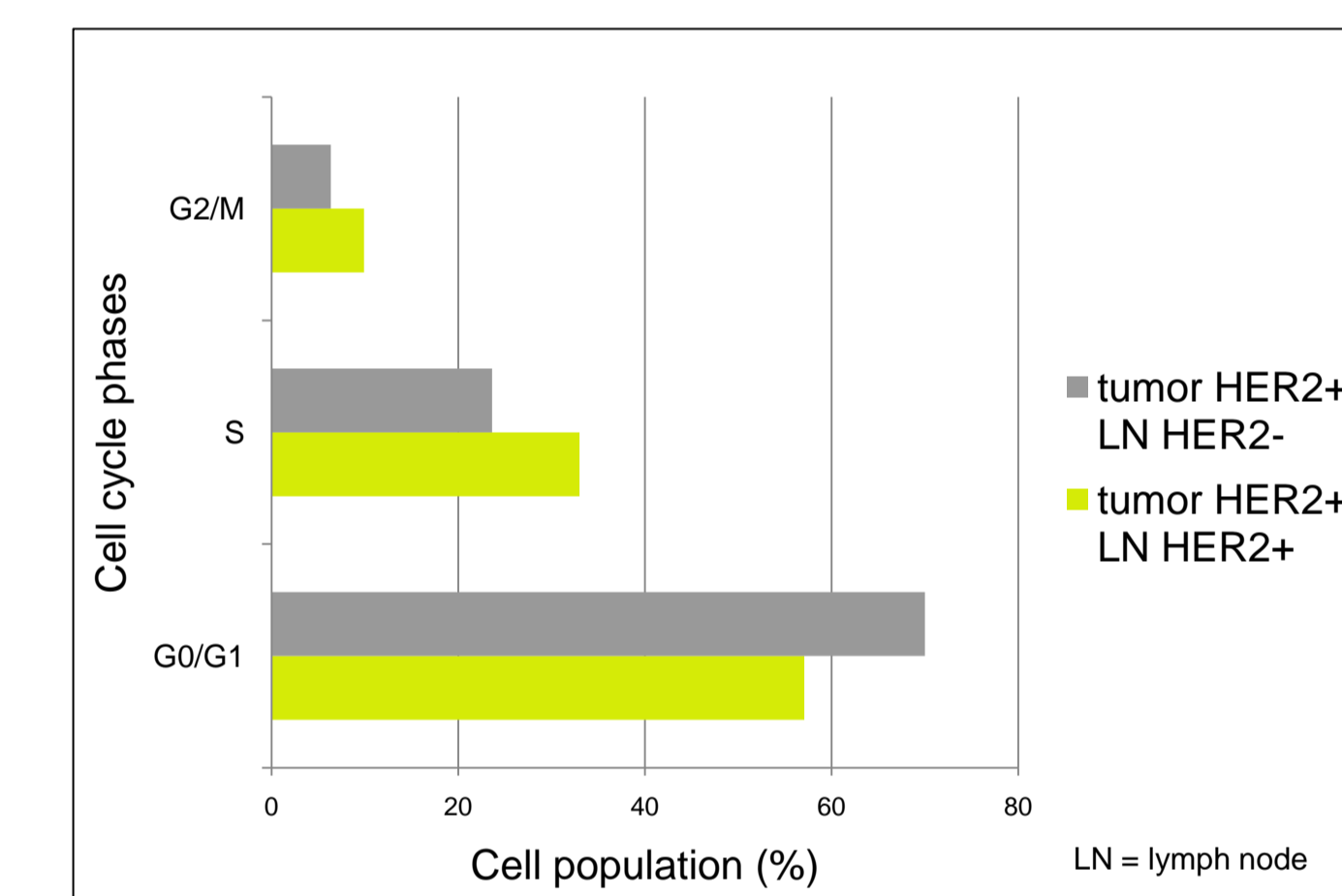
HER2 positive bladder carcinoma



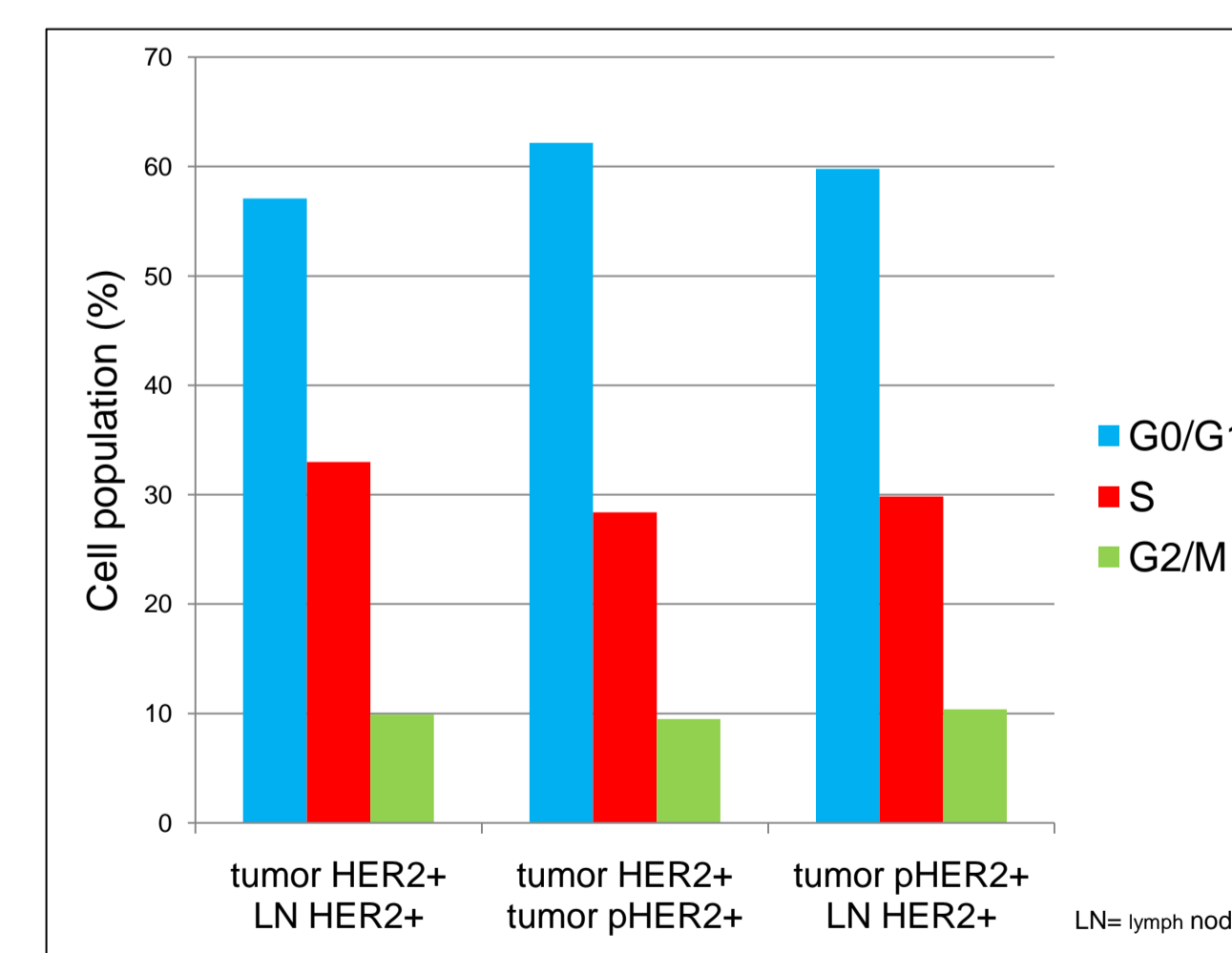
HER2 positive lymph node



pHER2 positive bladder carcinoma



- The cases HER2 positive for both tumors and lymph nodes had S-phase fraction and G2/M phase higher than cases HER2 positive for primary tumors and HER2 negative for lymph nodes (32,9% / 9,9% vs. 23,6% / 6,3%).



- The carcinomas with coexpression of HER2 and pHER2 had a similar value for G2/M phase with the group HER2 positive for both primary tumors and lymph nodes and also with the group pHER2 positive for tumors and HER2 positive for lymph nodes.

- HER2 overexpression was found in 12/21 primary bladder tumors and in 7/21 corresponding lymph nodes.

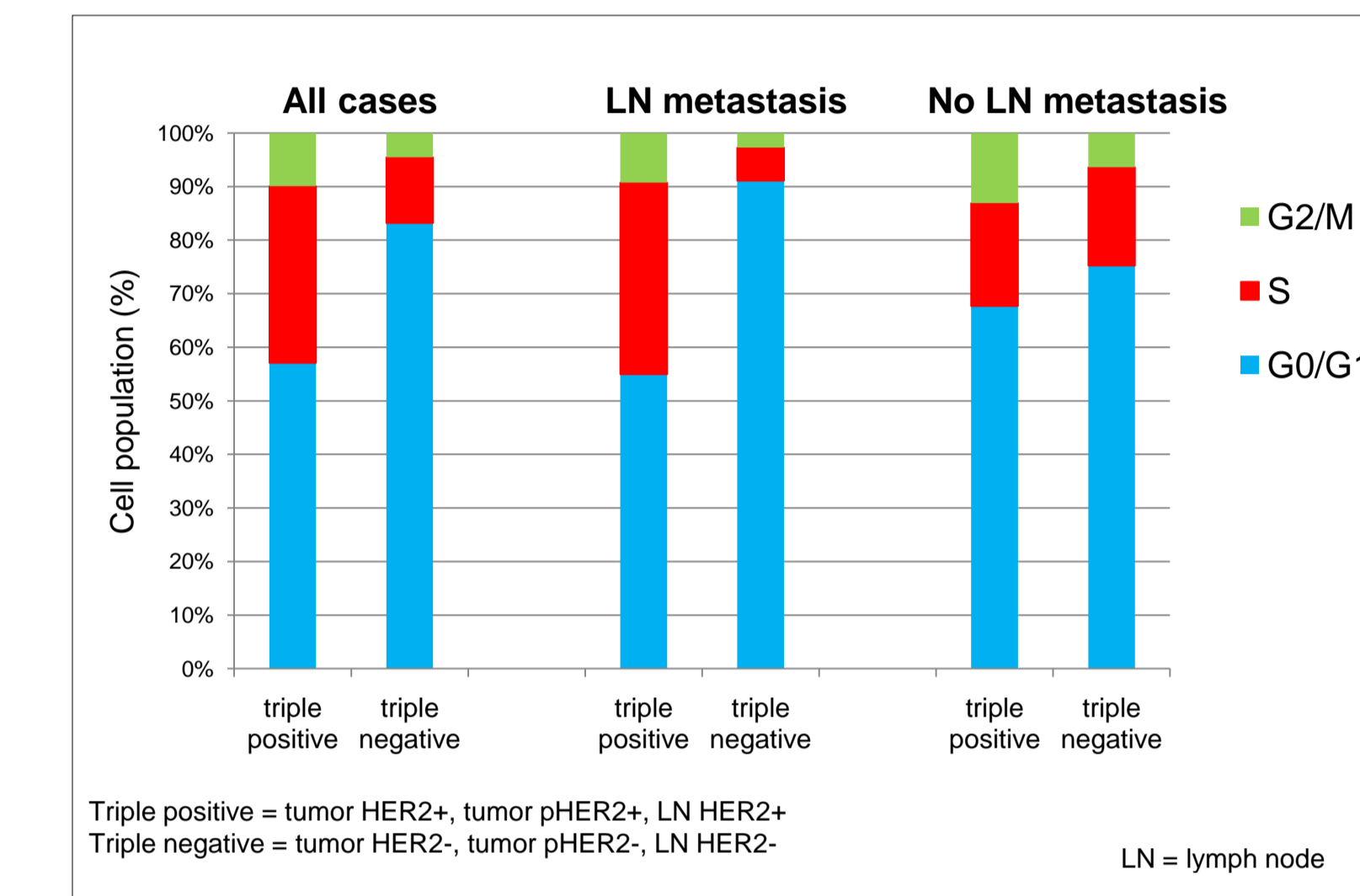
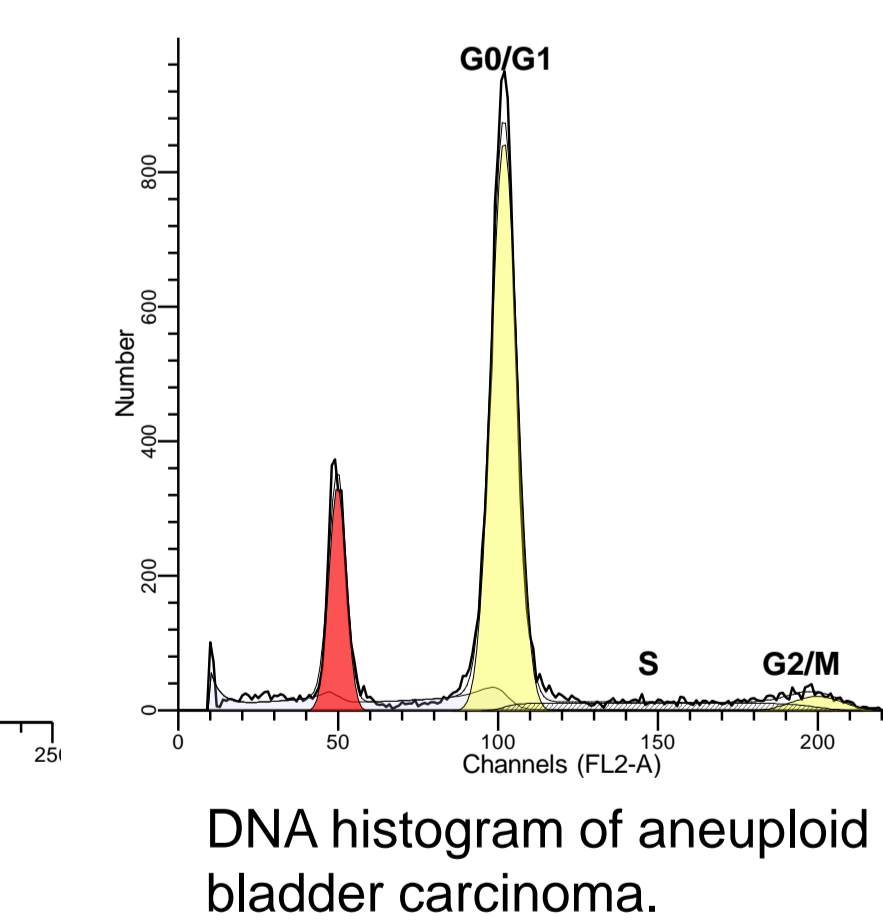
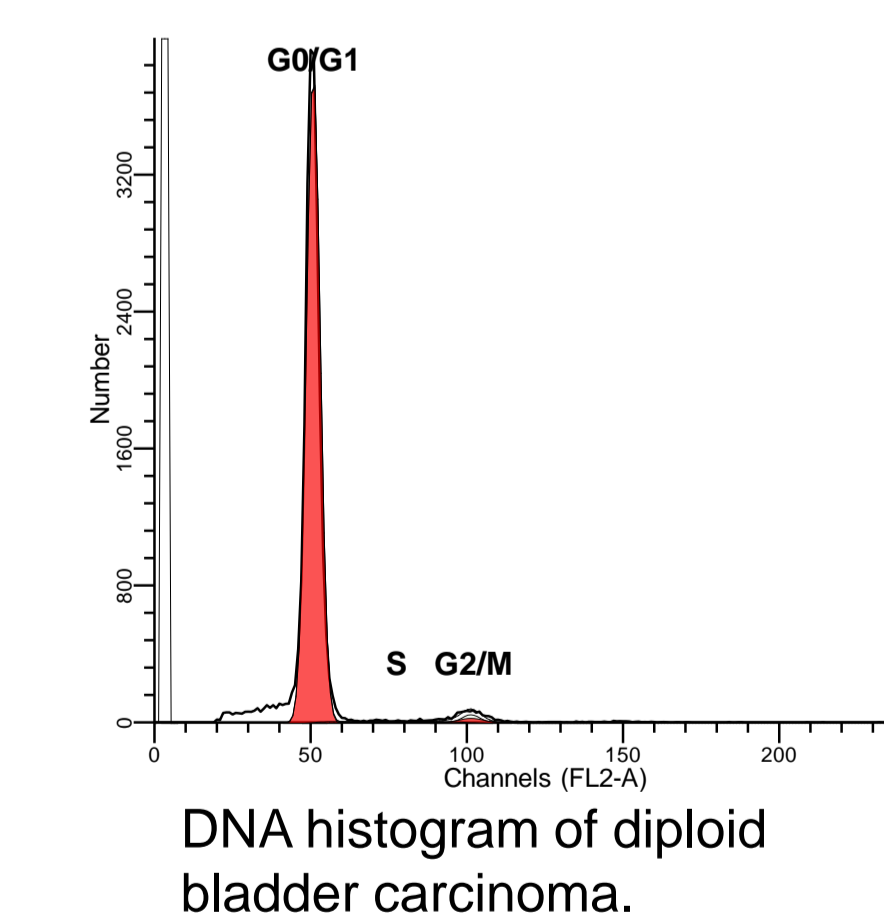
- pHER2 was expressed in 10/21 carcinomas.

- In the group with lymph node metastasis, 42% patients coexpressed HER2 and pHER2 in tumors and had HER2 positive expression in lymph nodes.

- The G2/M phase was higher in triple positive cases (with positive expression for HER2 and pHER2 in tumor and HER2 positive expression in lymph node) than in triple negative cases (with negative expression for HER2 and pHER2 in tumor and HER2 negative expression in lymph node).

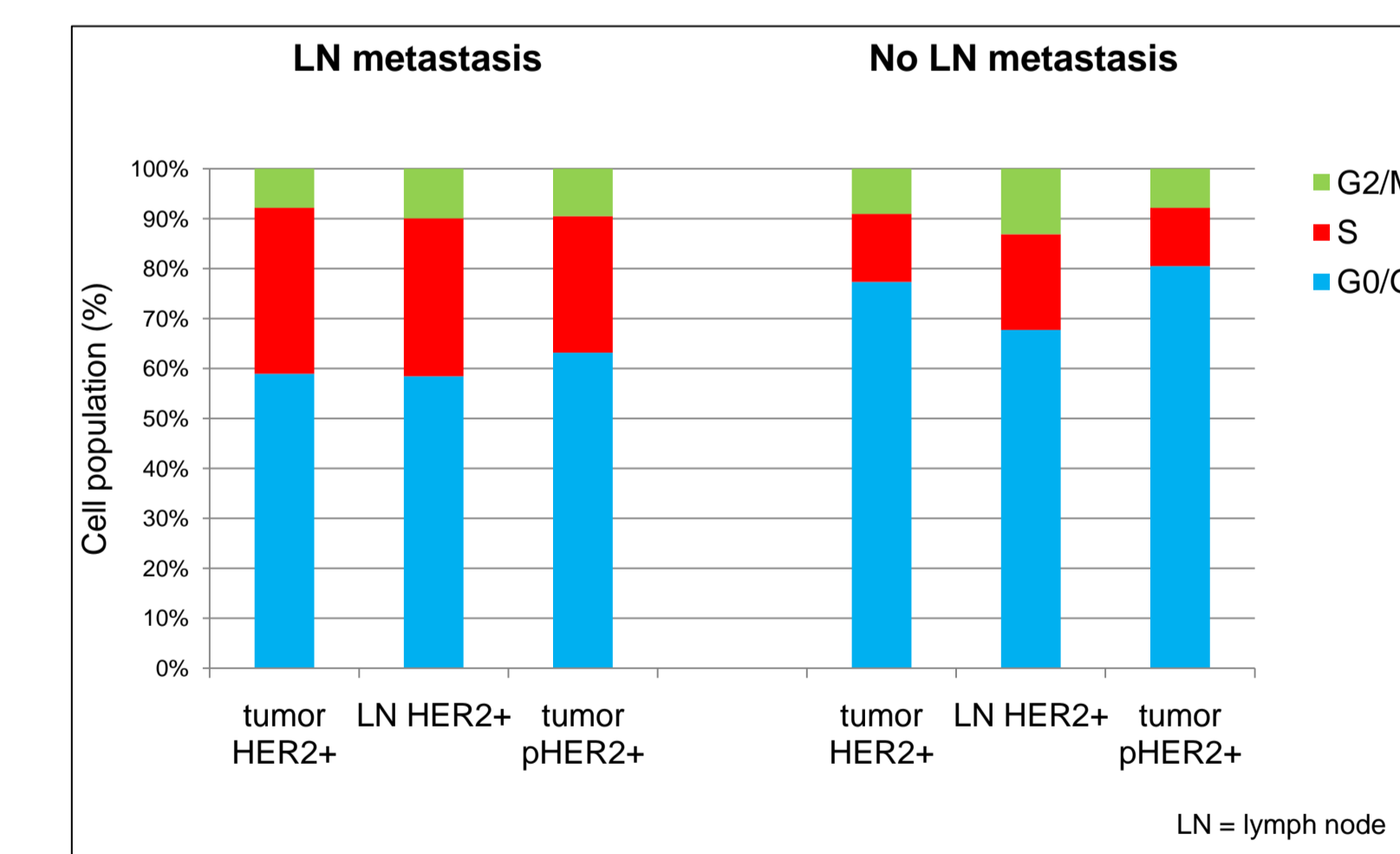
- Triple positive cases with lymph node metastasis had a higher S-phase fraction than those without metastasis (37,5% vs. 19,2%).

- In cases with HER2 overexpressed in tumor or in lymph node, S-phase fraction was higher in the group with lymph node metastasis than in the group without metastasis (33,2% vs.13,6% or 31,6% vs.19,2%).



- One case with HER2 negative primary tumor had paired lymph node with HER2 positive status.

- Five cases with HER2 protein overexpression in primary tumor had HER2 low score in the corresponding lymph node.



- All cases with lymph node metastases and triple positive were aneuploid.

- 5/6 cases HER2 positive in both tumor and paired lymph node were aneuploid.

## Conclusions

- The cases with coexpression of HER2 and pHER2 in primary tumor and HER2 positive lymph nodes seem to have a high rate of proliferation and a high metastatic potential.
- The evaluation of HER2 status in both primary tumors and paired regional lymph nodes may be useful in determination of the course of disease and for guide the development of useful therapies for patients with an aggressive behavior of bladder cancer.
- This study should be extended to clarify if HER2 status is changed during metastatic process, in bladder cancer.