Evaluation of Tumor Infiltrating Lymphocytes (TILs) in Invasive Breast Carcinoma

Guidelines for TILs assessment from the "International Immuno-Oncology Biomarker Working Group"

Authors: Carsten Denkert[1], Roberto Salgado[2] and Sandra Demaria[3]

1- Charité-University Hospital, Germany . 2-Institut Jules Bordet and TCRU, GZA, Belgium.

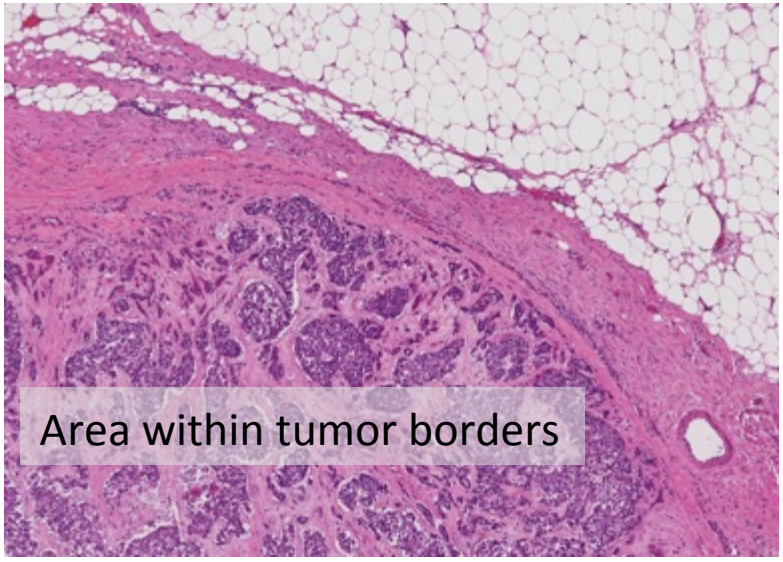
3-New York University Medical School, Perlmutter Cancer Center, USA.

Aim of this tutorial

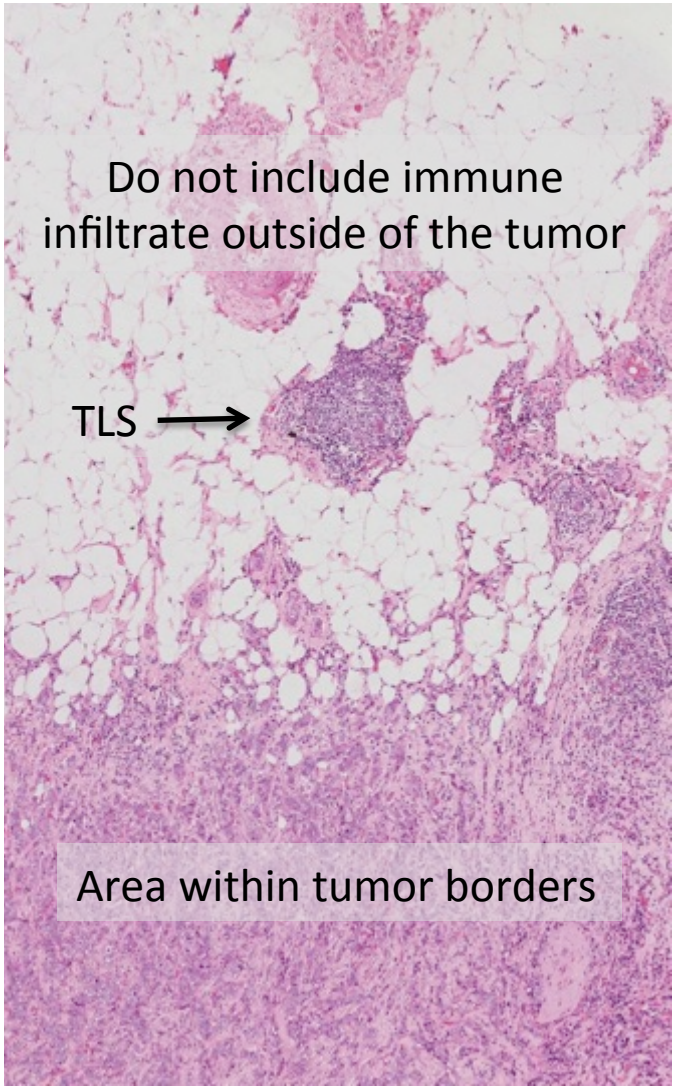
- To provide a guideline to pathologists for the standardized evaluation of tumor-infiltrating lymphocytes based on H&E slides of core biopsies or tumor resections.
- Please consult the manuscript for more specific details.

Step 1: Define area for TILs evaluation

- Only TILs within the borders of the invasive tumors are evaluated
- The invasive edge is included in the evaluation, but not reported separately
- Immune infiltrates outside of the tumor borders, e.g. in adjacent normal tissue or DCIS are not included



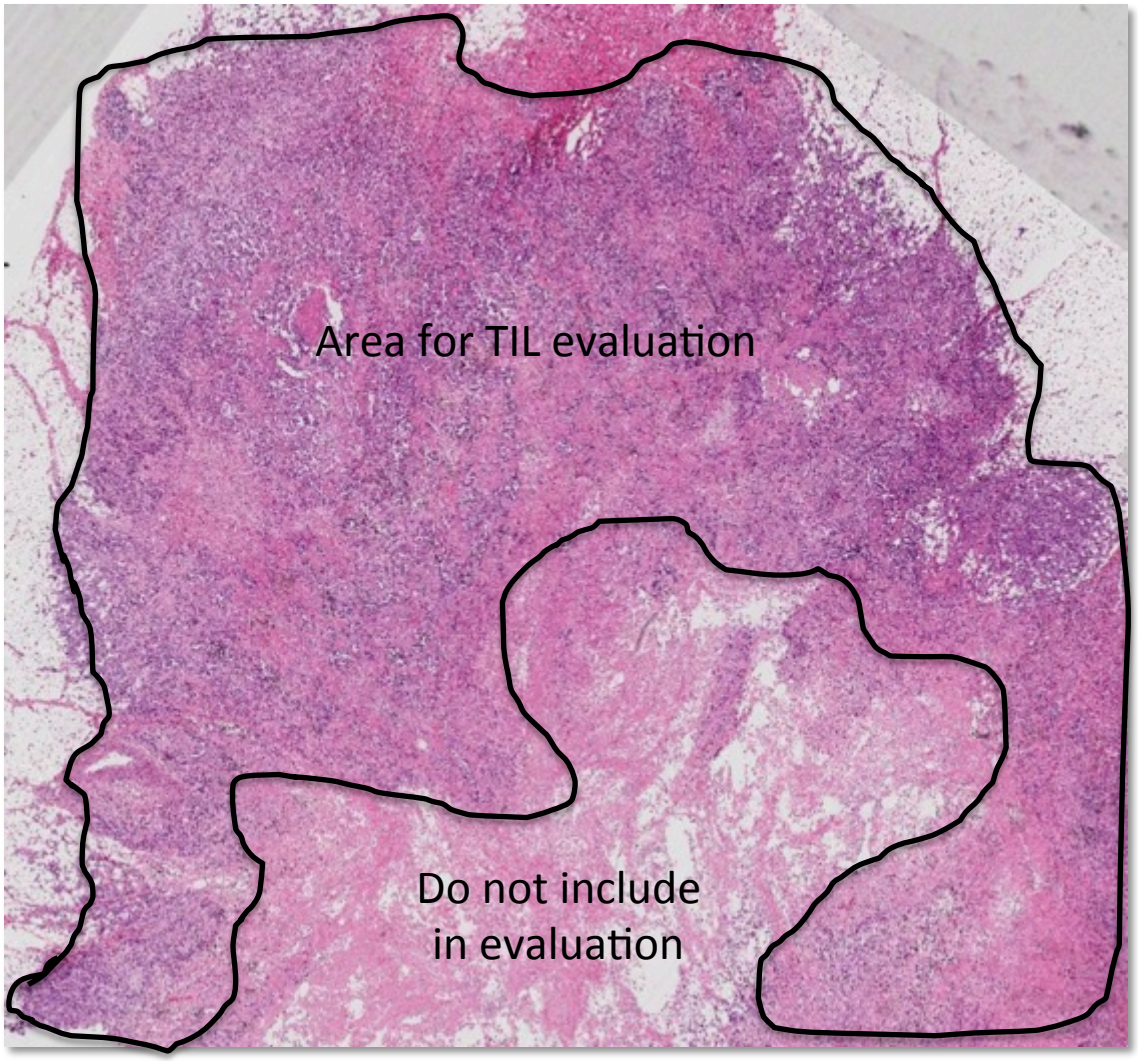
Example 1



Example 2

Step 1: Define area for TILs evaluation

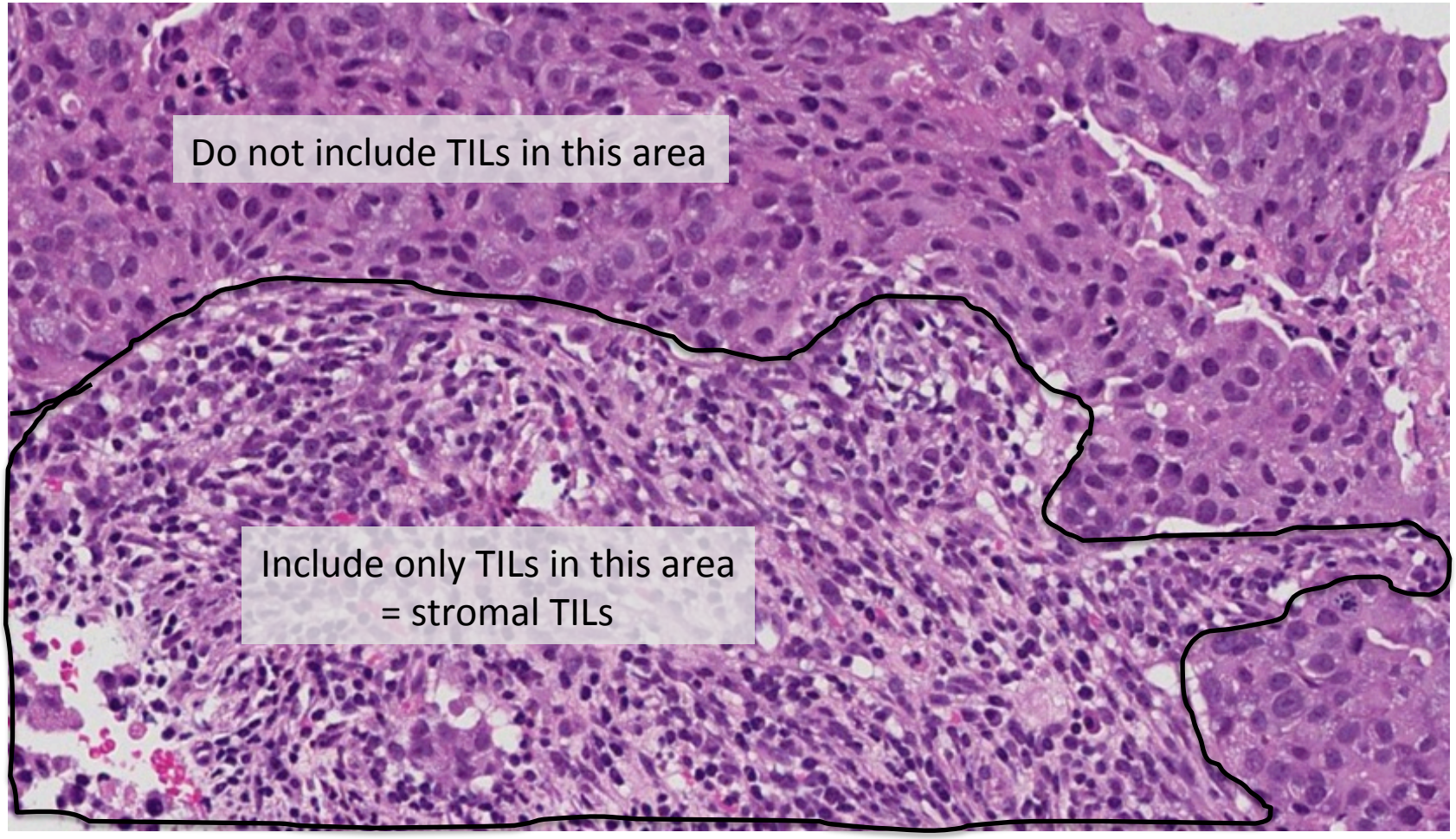
- Large areas of central necrosis or fibrosis are not included in the evaluation



Example 3

Step 2: Focus on stromal TILs

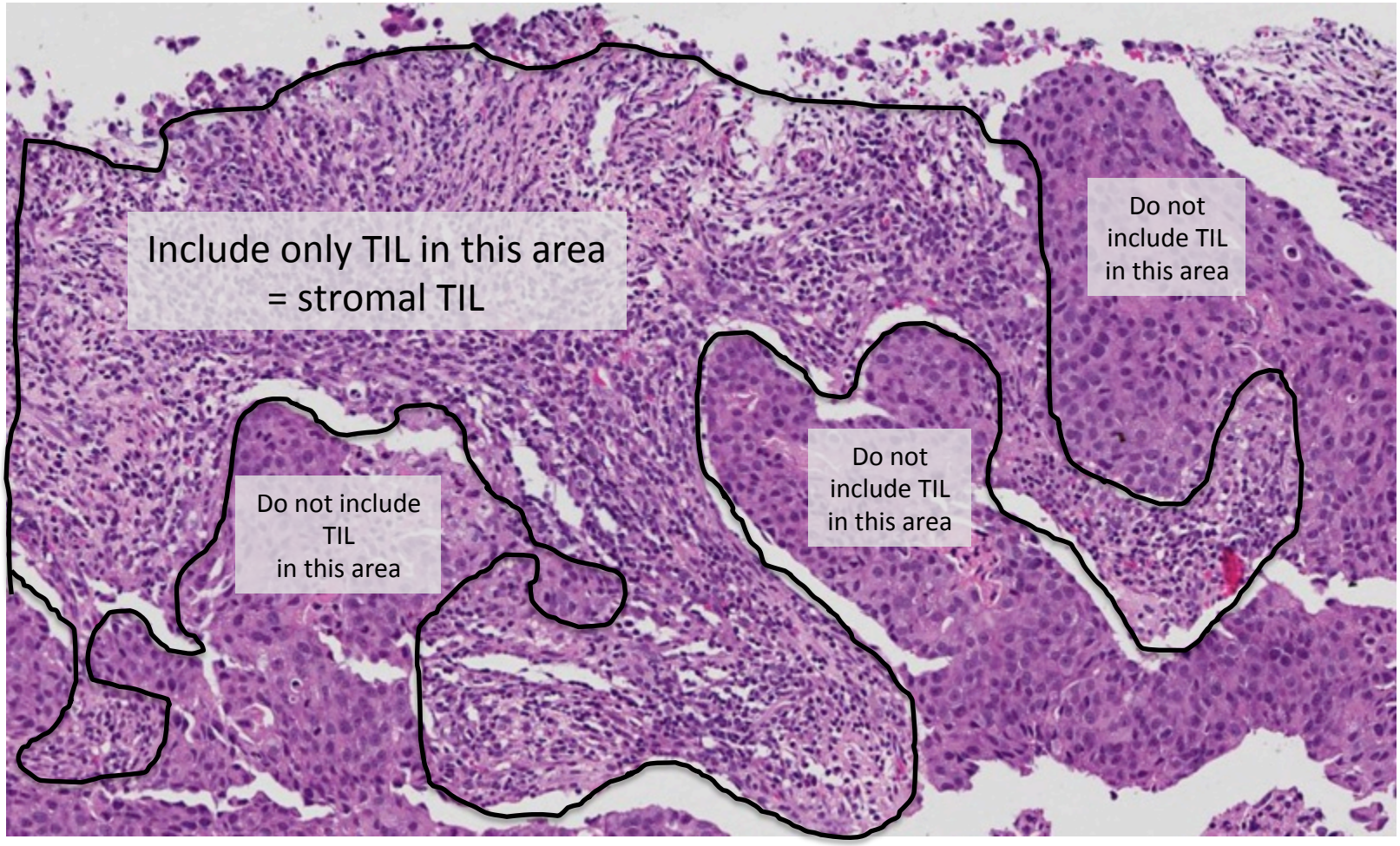
- In the diagnostic setting, only stromal TILs are relevant



Example 4

Step 2: Focus on stromal TILs

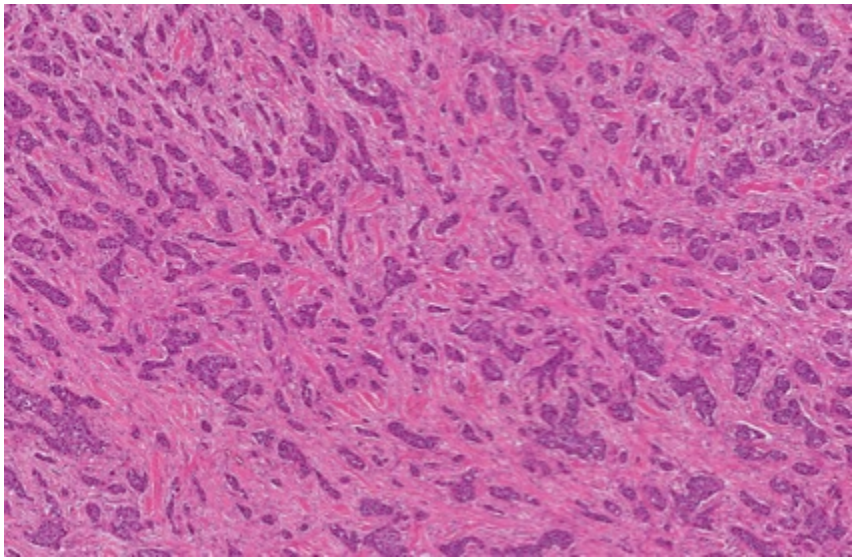
- In the diagnostic setting, only stromal TILs are relevant



Example 5

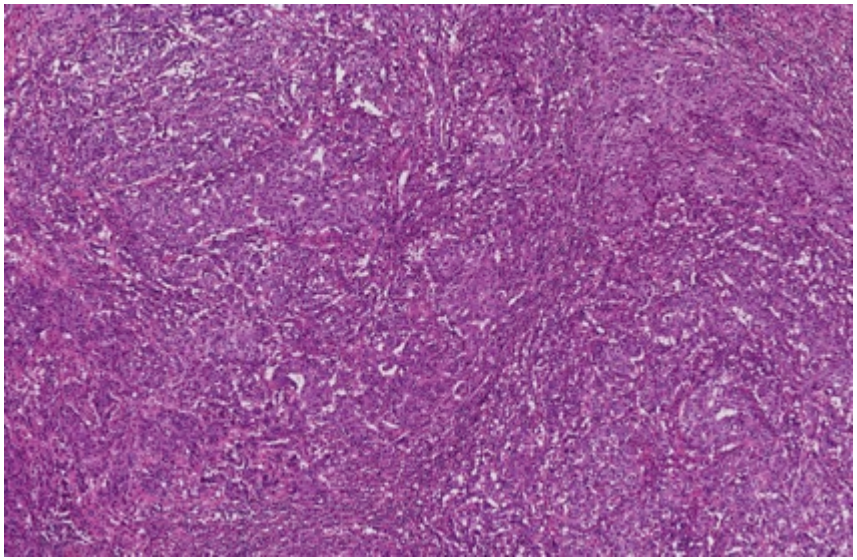
Step 2: Scan tumor at low magnification – focus on the tumor stroma

- Stroma contains predominantly collagenous tissue, few round cells



Example 6

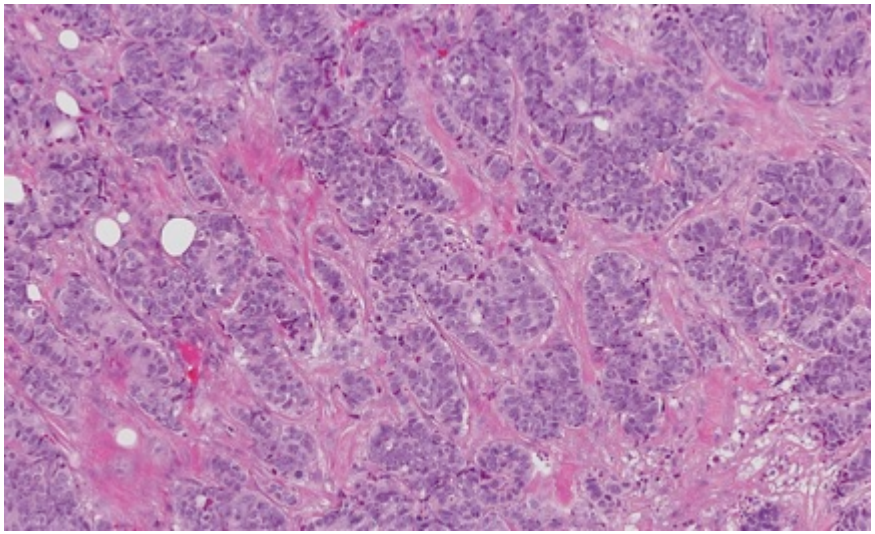
- Stroma contains predominantly round cell infiltrate, collagenous tissue difficult to recognize



Example 7

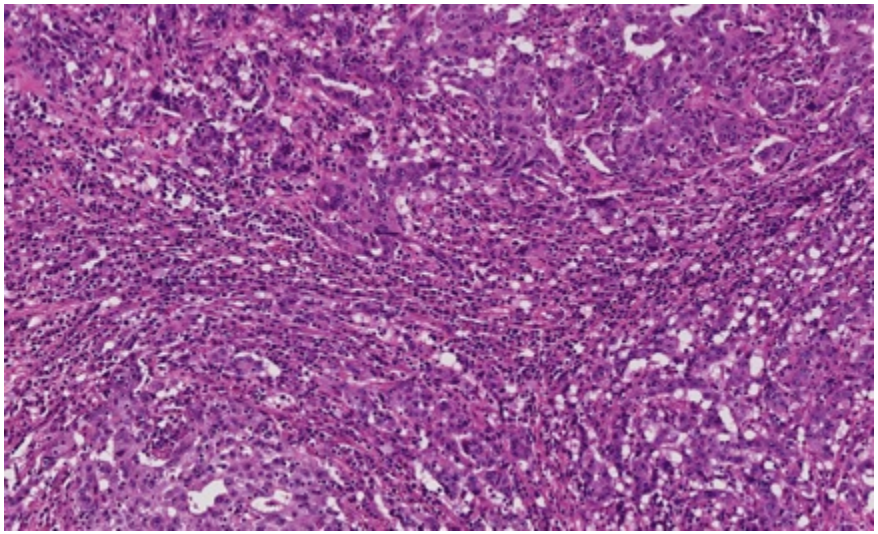
Step 2: Scan tumor at low magnification – focus on the tumor stroma

- Stroma contains predominantly collagenous tissue, few round cells



Example 8

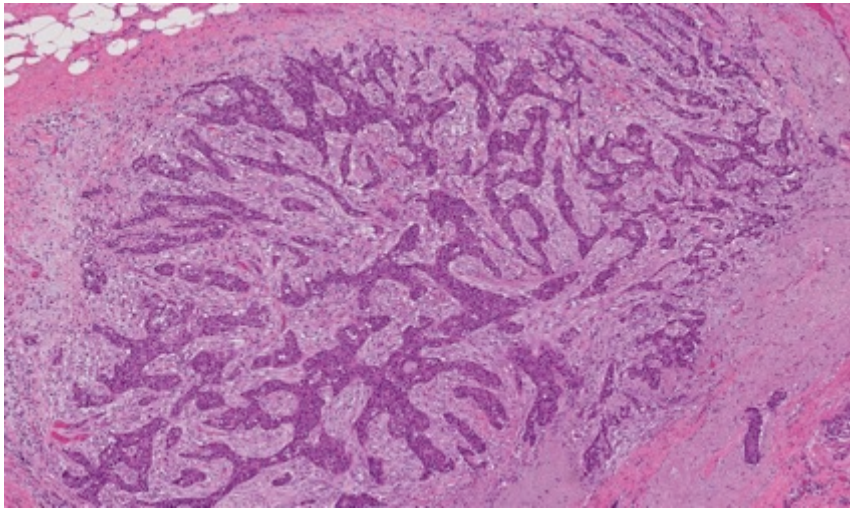
- Stroma contains predominantly round cell infiltrate, collagenous tissue difficult to recognize



Example 9

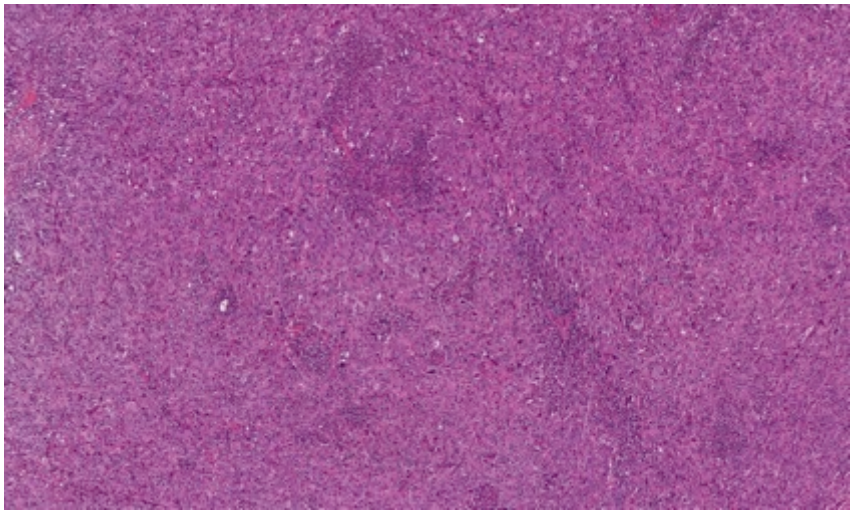
Step 2: Scan tumor at low magnification – focus on the tumor stroma

- Stroma contains predominantly collagenous tissue, few round cells



Example 10

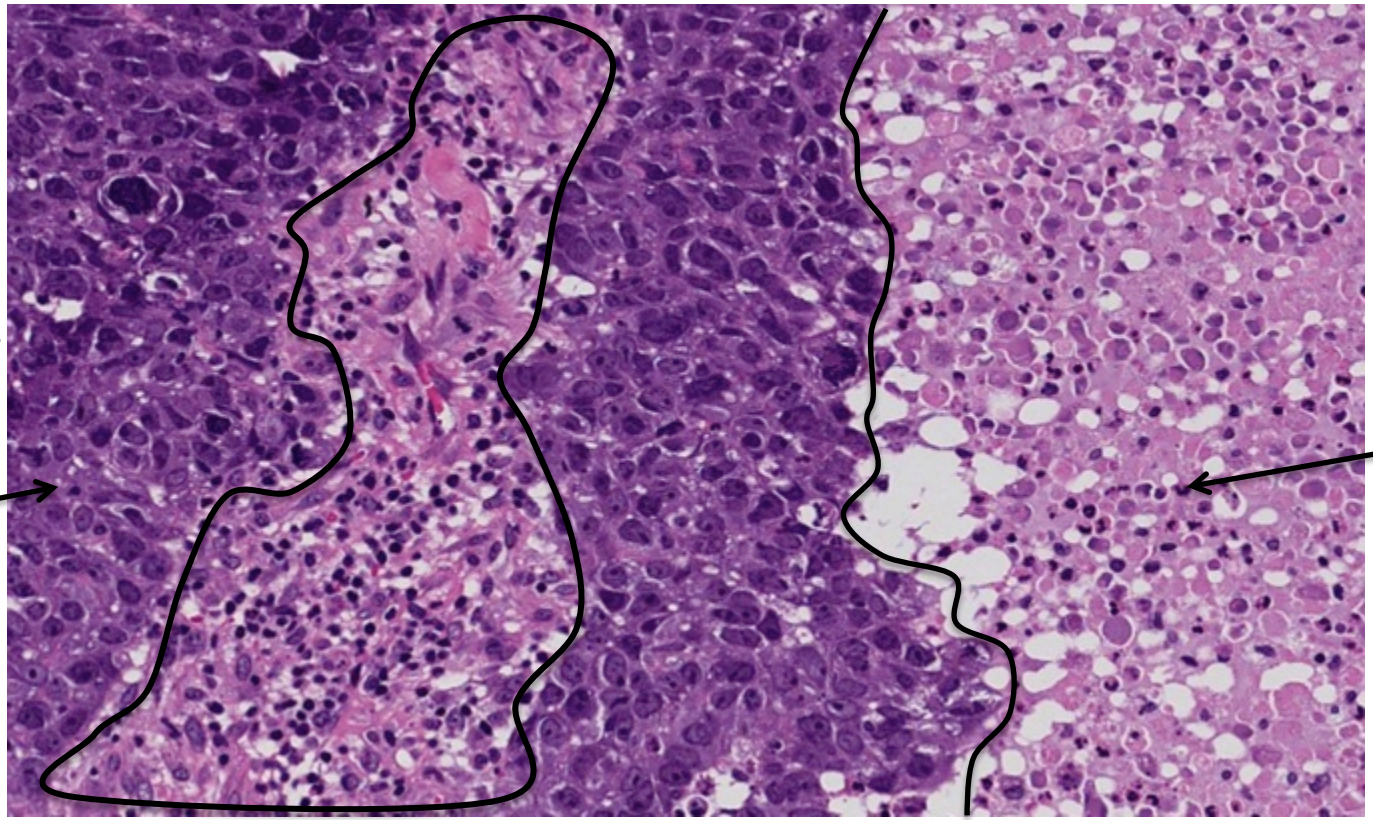
- Stroma contains predominantly round cell infiltrate, collagenous tissue difficult to recognize



Example 11

Step 3: Determine type of inflammatory infiltrate

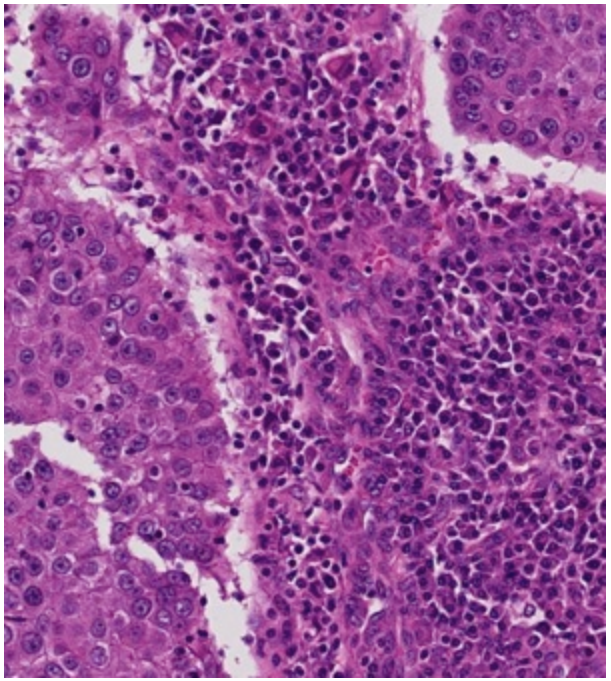
- Include only mononuclear infiltrate (lymphocytes & plasma cells)
- Do not include granulocytic infiltrate in areas of tumor necrosis



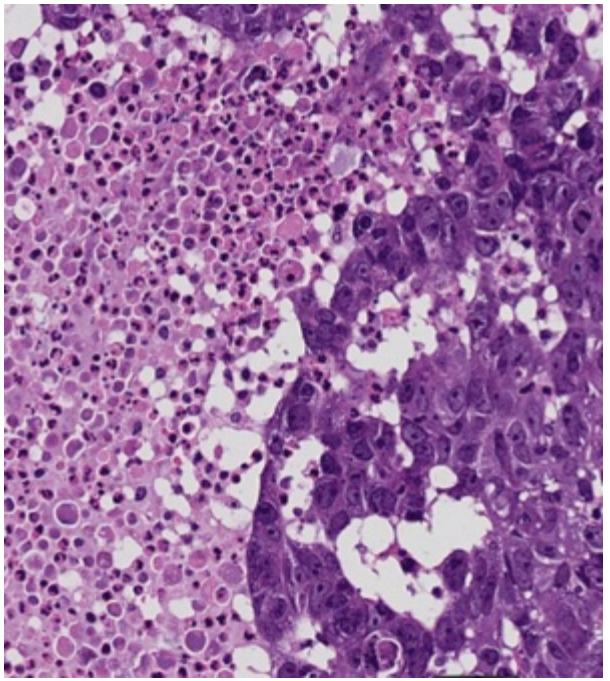
Example 12

Step 3: Determine type of inflammatory infiltrate

- Include only mononuclear infiltrate (lymphocytes & plasma cells)
- Do not include granulocytic infiltrate in areas of tumor necrosis



Example 13



Example 14

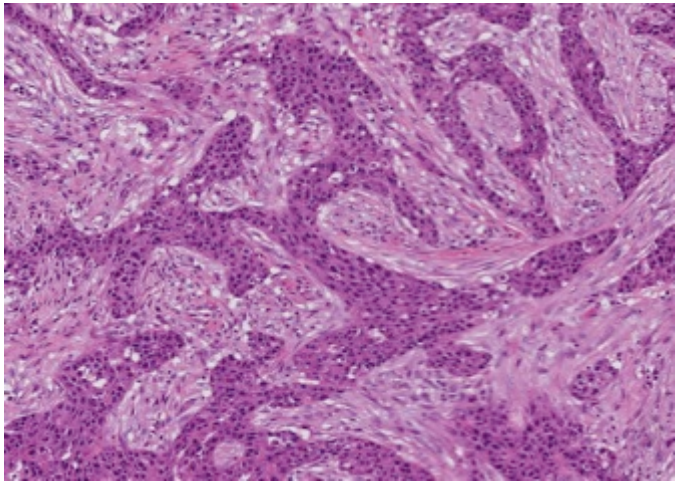
Step 4: As a first approach, include tumor in one of three groups based on low magnification and assess % stromal TILs (continue with Step 5 for percentage)

Group A: tumor with no/ minimal immune cells

Group B: tumor with intermediate / heterogeneous infiltrate

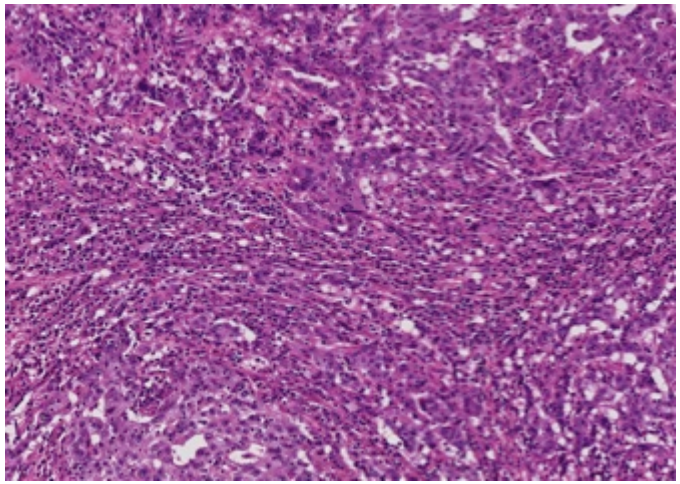
Group C: tumor with high immune infiltrate

0-10% stromal TILs | 10-40% stromal TILs | 40-90% stromal TILs



Example 15

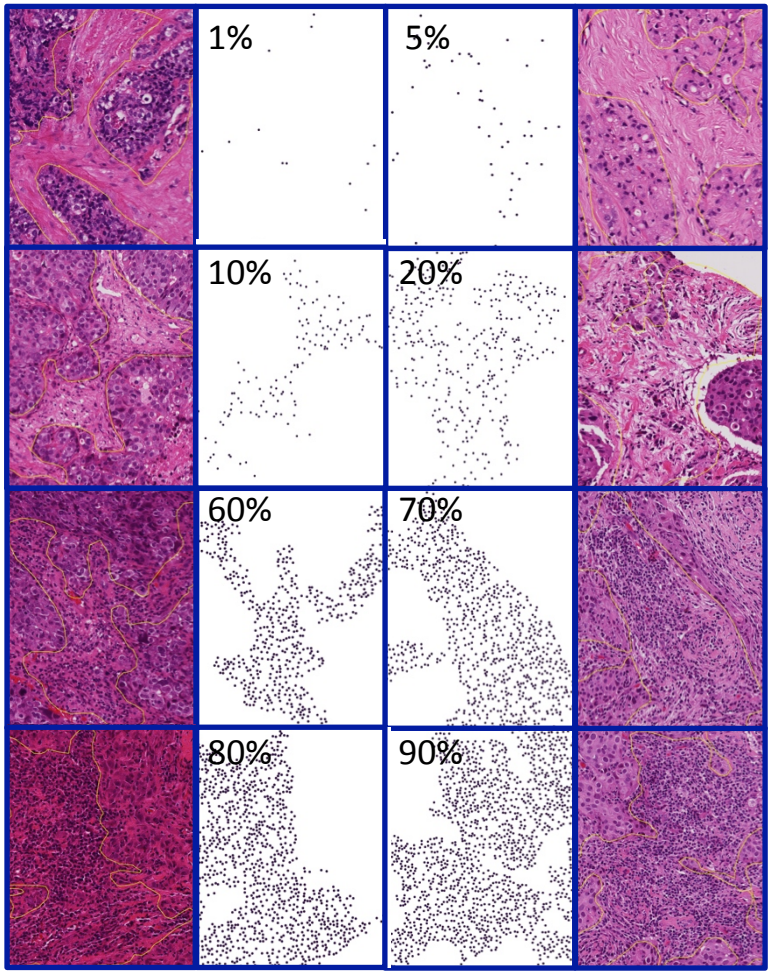
For this intermediate group evaluate different areas at higher magnification.



Example 16

The denominator used to determine the % stromal TILs is the area of stromal tissue (i.e. area occupied by mononuclear inflammatory cells over total intratumoral stromal area), not the number of stromal cells (i.e. fraction of total stromal nuclei that represent mononuclear inflammatory cell nuclei)

Step 5: Report percentage of stromal lymphocytes



- Report the average of the stromal area, do not focus on hot spots.
- For intermediate group evaluate different areas at higher magnification.
- Please note that lymphocytes do not form solid aggregates, therefore even with 90-100% stromal TILs there will still be some space between the individual lymphocytes.