189 Evaluating and Reporting Tumors after (Neo)adjuvant Therapy: Breast,Testis and Urinary Bladder

Fang Fan MD, PhD
Ivan Damjanov MD, PhD

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The new demands and responsibilities for pathologists in evaluating and reporting tumors after neoadjuvant therapy makes it imperative for us to understand the expectations and follow guidelines in dealing with post-therapy specimens. In this course, we will review the current consensus recommendations and summarize our experience for handling post-therapy breast specimens (part I), and post-therapy specimens of metastatic testicular germ cell tumors and urinary bladder (part II). We will describe typical therapy related changes in tumors and normal tissues, and show how to include these findings in standardized pathology reports. Important diagnostic problems and potential pitfalls in diagnosing therapy related changes will be discussed together with the current consensus recommendations for reporting tumors exposed to neoadjuvant therapy. Following the review, we will use a case-based approach to analyze individual cases using the strategies discussed in the review part of the presentation. We will discuss potential pitfalls, share our lessons learned from these cases and recommend the optimal strategies for handling similar situations. This course provides practical guidelines for pathology work-ups of post-therapy tumors. Participants will benefit from attending this course by comparing, reviewing, modifying and hopefully improving their own practice and thus relate new information to their daily work.

- Define neoadjuvant chemotherapy of breast cancer; describe how malignant germ cell tumors of testis and bladder urothelial carcinoma are managed clinically.
- Discuss how to handle breast specimens after neoadjuvant chemotherapy, including the evaluation of residual tumor, margin status, and axillary lymph nodes; list the most important parameters that must be included in the pathology report of breast cancer after neoadjuvant chemotherapy.
- Describe various morphologic features of metastatic germ cell tumors after chemotherapy, and learn how to use the correct reporting terminology that has defined clinical implications; describe the spectrum of therapy-induced pathologic changes in urinary bladder important for evaluating treatment effects and for differential diagnosis with residual or recurrent malignancy.

FACULTY:

Fang Fan MD, PhD
Ivan Damjanov MD, PhD

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Evaluating and Reporting Tumors after (Neo)adjuvant Therapy: Breast, Testis and Urinary Bladder

Ivan Damjanov, MD, PhD
Fang Fan, MD, PhD
Department of Pathology and Laboratory Medicine
University of Kansas Medical Center
Kansas City, Kansas

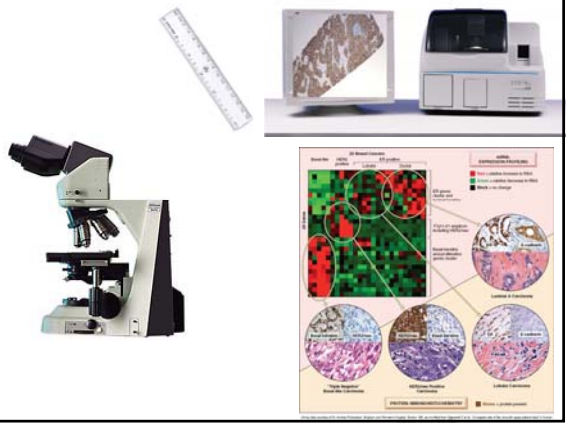
Conflict of Interest Disclosures

- The speakers do not have any conflict of interest disclosures.

Outlines

- Brief Introduction
- Breast
- Testis
- Urinary Bladder
- Questions and Answers

Pathology Before



Introduction

- Advancement in medicine and science
  - Better understanding of disease
  - More treatment options
- Pathologists play a key role
  - Not a simple diagnosis any more
  - Provide prognostic and predictive informations

Introduction

- Traditionally - Post-operative or adjuvant chemotherapy:
  - The patient receives chemotherapy after complete surgical removal of the tumor.
- Now - Pre-operative or neoadjuvant chemotherapy:
  - The patient receives chemotherapy before complete surgical removal of the tumor.

Introduction

- Neoadjuvant vs. adjuvant chemotherapy
  - Survival is equivalent
- Advantages
  - Reduce tumor size to increase resectability
  - Measure the response of tumor to chemotherapy in vivo
  - Not delaying chemotherapy
  - Predict long-term outcome

Introduction

- The response to treatment is monitored clinically and radiologically.
- Pathologic assessment is the gold standard for determining treatment response.

Introduction

- Pathologist encounter the following issues
  - Tumor response to therapy
  - Therapy-related changes in the morphology of primary or metastatic tumor
  - Therapy-related changes in normal tissues
- What informations need to be included in the pathology reports in these post-therapy specimens?

Evaluating and Reporting Breast Cancer after NACT

- **Introduction**
- **Evaluating and reporting**
  - **Breast**
  - **Lymph nodes**
- **Predictive factors in NACT of breast carcinomas**

Changes in Breast Cancer Management

- **Lumpectomy plus radiation vs modified radical mastectomy**
- **Sentinel lymph node biopsy vs axillary lymph node dissection**
- **Neoadjuvant chemotherapy vs adjuvant chemotherapy**

NACT Rationale

- Complete evaluation of breast cancer before surgical removal is greatly improved.
  - Breast imaging
    - Mammogram, sonogram, MRI
    - Determination of tumor size
  - Image guided core needle biopsies
    - Stereotactic core needle biopsy (mammographic guidance)
    - Sono-guided core needle biopsy
  - Fine needle aspiration/core needle biopsy of an enlarged node
    - Nodal staging

- Biological rationale
  - Invasive cancer is a systemic disease
  - Animal studies
  - Clinical trials

- The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial
  - 1523 patients with early stage, operable breast carcinoma were randomized to receive four cycles of AC either before or after surgical treatment.
  - The primary end points were disease-free and overall survival.
  - After 9 years, the overall survival and disease-free survival were nearly identical between the two groups.

Fisher B, Brown A, et al. J Clin Oncol 1997; 15:2483-93.
Fisher ER, Wang J, et al. Cancer 2002; 95: 681-695.

- A second large trial was performed by the European Organization for Research and Treatment of Cancer (EORTC)
  - 698 patients were randomized to preoperative or postoperative chemotherapy
  - Like the NSABP B-18 trial, the EORTC study demonstrated equivalent survival and rates of distant metastases between the two groups.

Van der Hage JA, Cornelis JH, et al. J Clin Oncol 2001; 19: 4224-4237

- Neoadjuvant vs. adjuvant chemotherapy
  - Survival is equivalent
- Potential advantages were discovered in these trials
  - 27% of the patients in the B-18 trial and 23% of the patients in the EORTC trial for whom mastectomy was originally planned were able to have a lumpectomy after the neoadjuvant chemotherapy
  - The ability of measuring the response of tumor to chemotherapy

Comparison Between Neoadjuvant and Adjuvant Therapies: Risks and Benefits

- Disease-free survival (DFS) and overall survival (OS) are equivalent in patients treated with the same adjuvant or neoadjuvant chemotherapy regimen.[1]
- Neoadjuvant therapy can be offered to candidates for adjuvant therapy, regardless of tumor size
- Neoadjuvant therapy has the following clinical advantages:[2]
  - Improves surgical options
  - Response to neoadjuvant therapy is a predictor of long-term outcome
    - Pathologic CR correlates with improved DFS and OS

1. Mauri D, et al. *J Natl Cancer Inst*. 2005;97:188-194.
2. Kaufmann M, et al. *J Clin Oncol*. 2006;24:1940-1949.

NCCN® Guidelines Recommend that Neoadjuvant Therapy Be Considered to Improve Surgical Options in Candidates for Adjuvant Therapy

- Neoadjuvant therapy may improve resection options in patients with locally advanced breast cancer
  - To allow for breast conserving surgery or to make inoperable tumors resectable
- Recommended adjuvant regimens are appropriate to consider in the neoadjuvant setting
  - (e.g., endocrine therapy, trastuzumab, chemotherapy)

NCCN Clinical Practice Guidelines. Breast Cancer. V.2.2011.

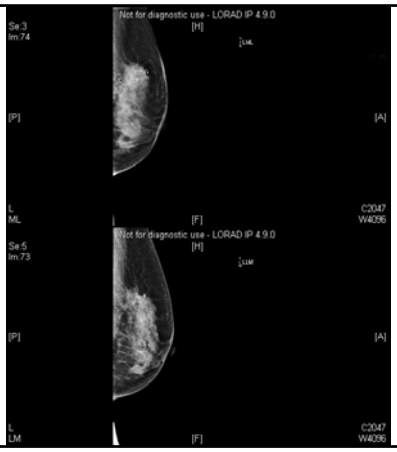
Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed 19 April 2011.

Before NACT

- Pre-treatment Diagnosis
  - **Core needle biopsy**
    - A diagnosis of invasion must be made with certainty
    - This may be the only tumor tissue we have on the patient
  - **Pathology report should include:**
    - Histologic type
    - Nuclear grade
    - Histologic grade
    - ER, PR, Her-2, Ki-67

During NACT

- The response to treatment is monitored clinically and radiologically.
  - A complete clinical response is defined as complete disappearance of all clinically detectable disease.
  - A partial response requires a >50% reduction in the sum of the products of the 2 longest perpendicular diameters of measurable tumor deposits.
  - Progressive disease is defined as a 25% increase in the sum of the products of the 2 longest perpendicular diameters of measurable tumor deposits or the appearance of new lesions.



- Complete clinical regression does not imply complete pathological regression!
- Between 30-50% of patients with a clinical CR will have residual breast cancer detected by the pathologist in the surgical specimens.
- About 20% of patients with clinically suspected residual disease will have a pathological complete response (pCR) on microscopic examination.
- **Pathologic assessment is the gold standard for determining a complete response.**

Schwartz GF, Hortobagyi GN, et al. Hum Pathol 2004; 35: 781-784.

Pathological Complete Response (pCR)

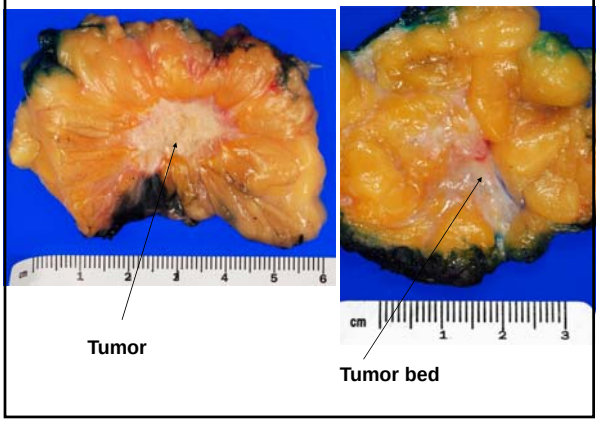
- **Pathologic complete response is defined as the absence of invasive cancer in the breast and axilla; DCIS may be present.**
- Pathological complete response (in breast and axilla) is an excellent surrogate marker of improved disease free and overall survival and is therefore one of the goals of neo-adjuvant chemotherapy.
- The most powerful predictor of long-term outcome is the extent of residual disease present after NACT.

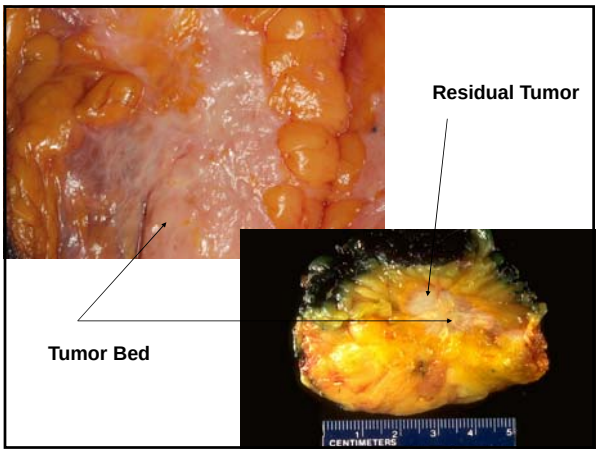
Pathologic Examination After NACT

- Prior to examination
  - **Determine if a patient has received NACT**
    - **Should be provided in the clinical history (good luck!)**
    - **Clues: long interval between the previous core needle biopsy and current resection (4-6 months); no palpable/visible tumor in the current specimen**
    - **Always confirm with the clinician if uncertain**
  - **Always check the radiology report**
    - **The location of tumor (sometimes multiple foci)**
    - **The radiologic response of the tumor to therapy**

Pathologic Examination After NACT

- Gross examination
  - **It's all about identifying the tumor bed**
  - **It's imperative to identify the tumor bed**
  - **The tumor bed appears as an irregular area of rubbery fibrous tissue**



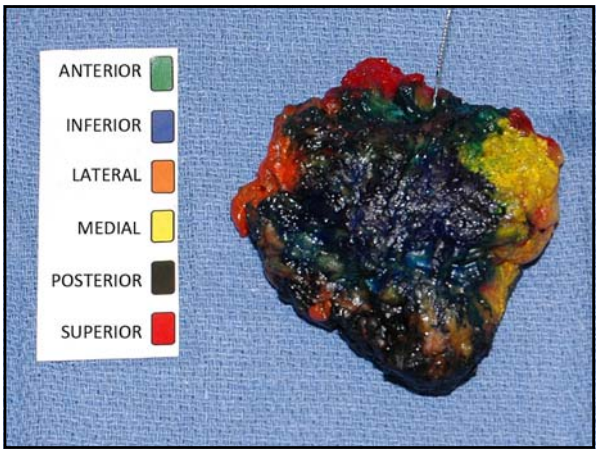


Pathologic Examination After NACT

- Gross examination
  - Finding the tumor bed can be challenging after a substantial clinical response
  - Use prior clinical and radiological information, and identify the CLIP!
    - **Lumpectomy: always obtain a specimen radiograph to demonstrate the clip to ensure excision of the tumor bed**
    - **Mastectomy: specimen radiograph may be needed to help identifying the clip**

Pathologic Examination After NACT

- **Sampling**
- **Lumpectomy**
  - **Ink the margins (4 or 6 colors)**
  - **If the specimen is not large**
    - **Submit all**
  - **If no tumor bed is identified grossly**
    - **Submit all**
  - **If the specimen is big, and tumor bed is identified grossly**
    - **Submit the entire tumor bed**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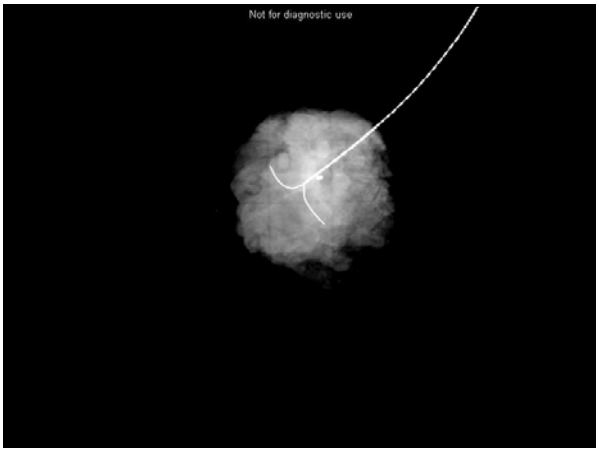
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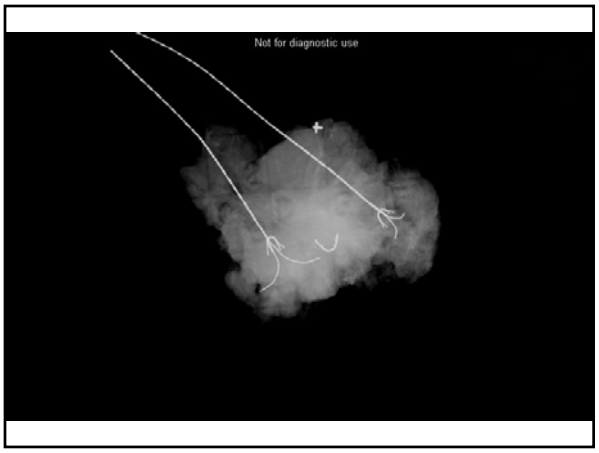
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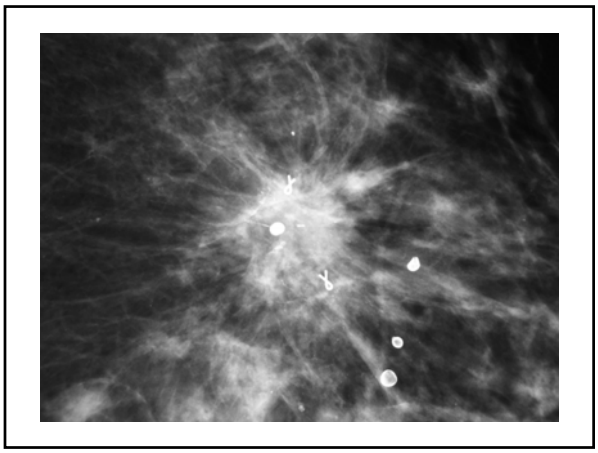
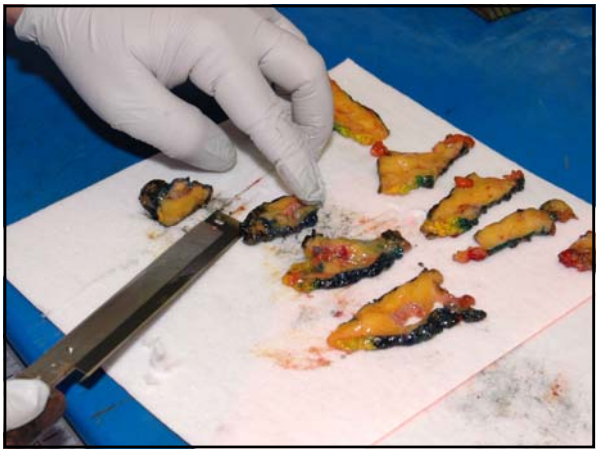
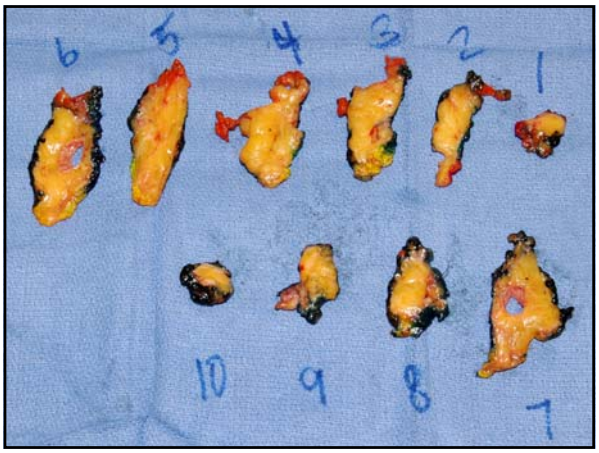
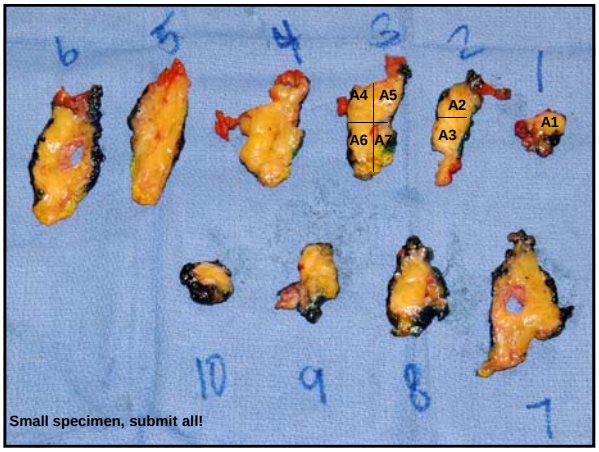
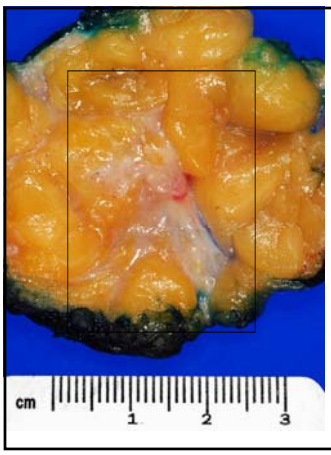




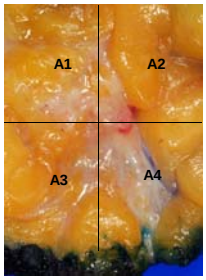




Small specimen, submit all!

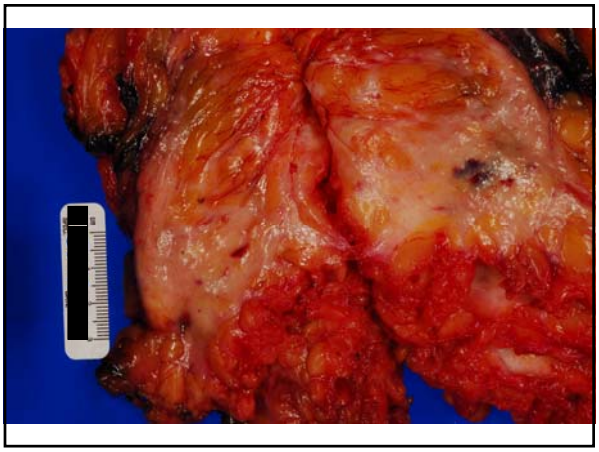


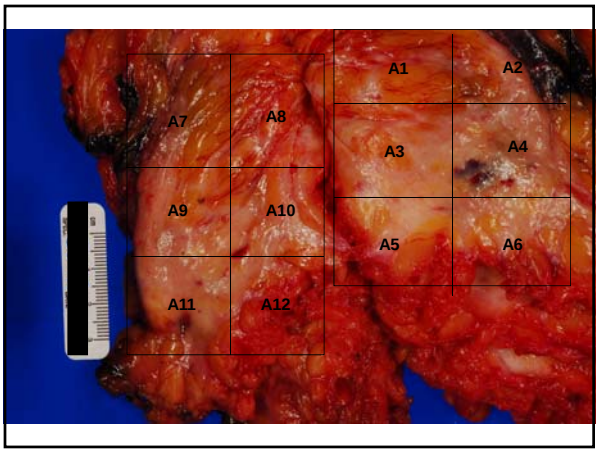
Large specimen, submit the entire tumor bed as sequential slices. Slice 1: A1-A4, slice 2: A5-A8, etc.

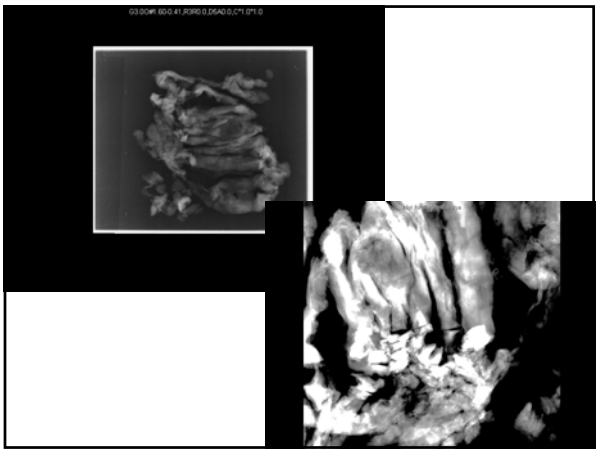


Pathologic Examination After NACT

- **Sampling**
  - **Mastectomy**
    - **Ink the posterior margin**
    - **If the tumor bed is identified grossly**
      - **Small tumor bed: submit all**
      - **Large tumor bed: Submit at least two entire slices of the tumor bed area, then representative sections of the dense area; if no residual tumor found, may need to submit all.**
    - **If no tumor bed or clip is identified grossly**
      - **X-ray the specimen to identify the clip**
      - **Submit around the clip according to the pretreatment tumor size**

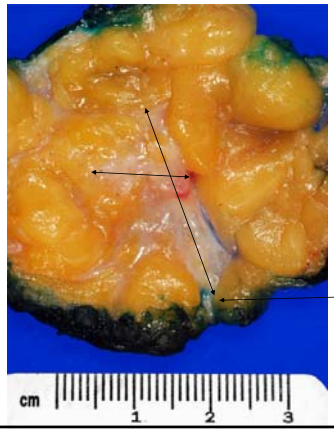






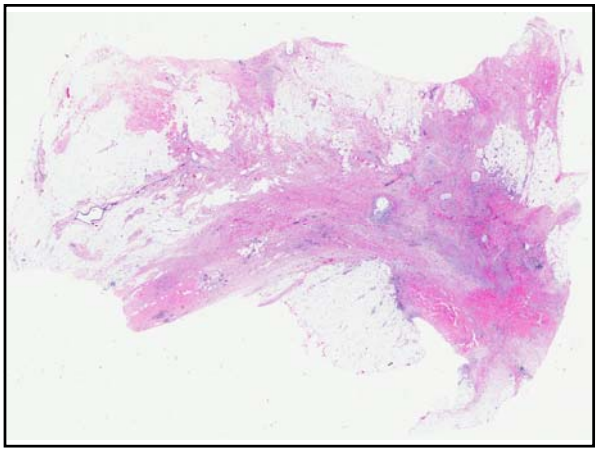
Pathologic Examination After NACT

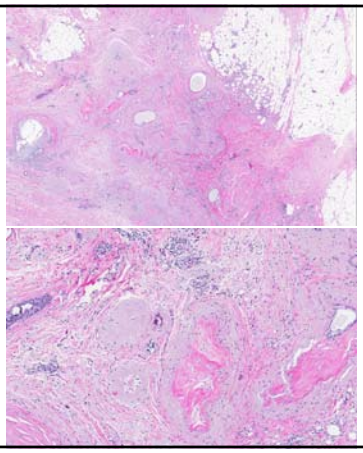
- **Gross measurement**
  - **Specimen size**
  - **Tumor bed size**
  - **Residual viable tumor nodule (if present) size**
  - **The distance of tumor bed to all margins**

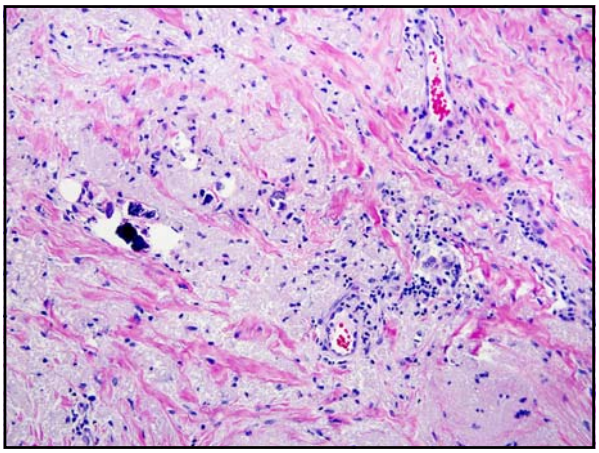


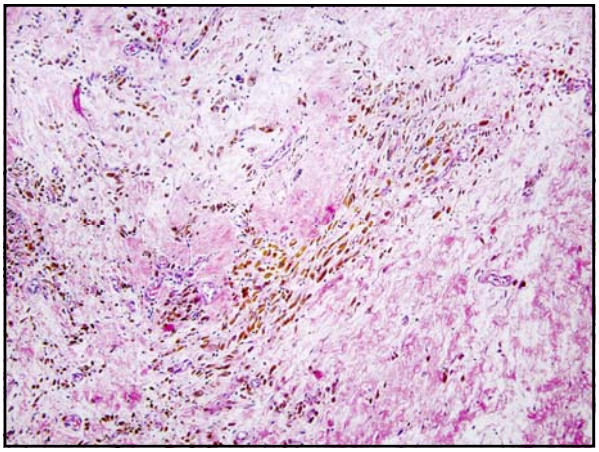
Pathologic Examination After NACT

- Microscopic examination
  - **Tumor bed**
    - **Hyalinized stroma, edema, fibroelastosis, patchy aggregates of lymphocytes, foamy histiocytes, hemosiderin deposition**



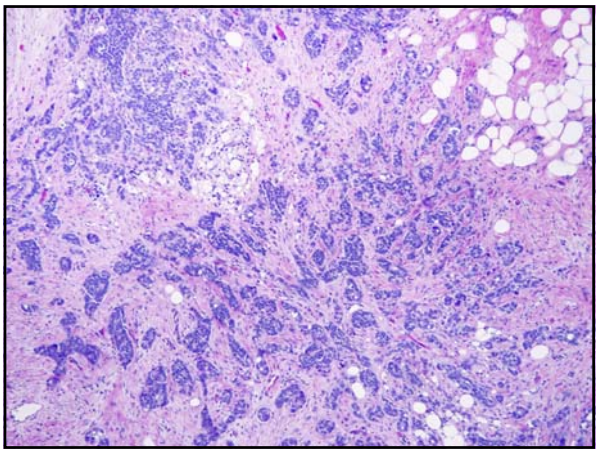


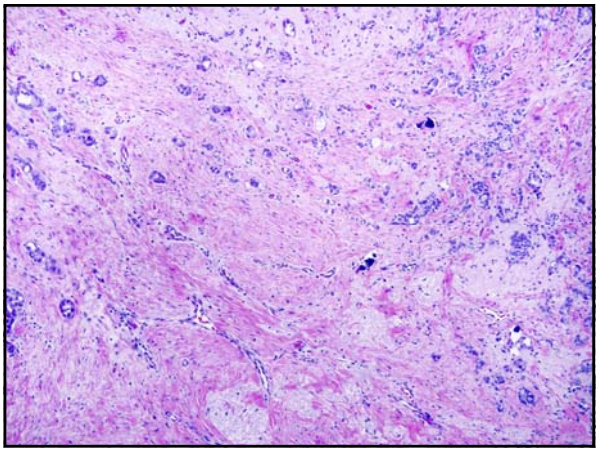


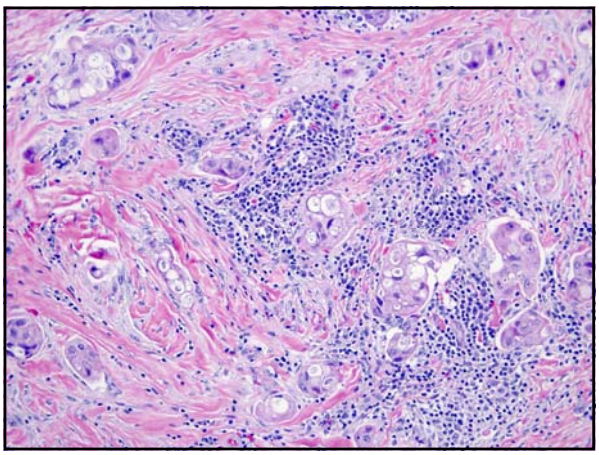


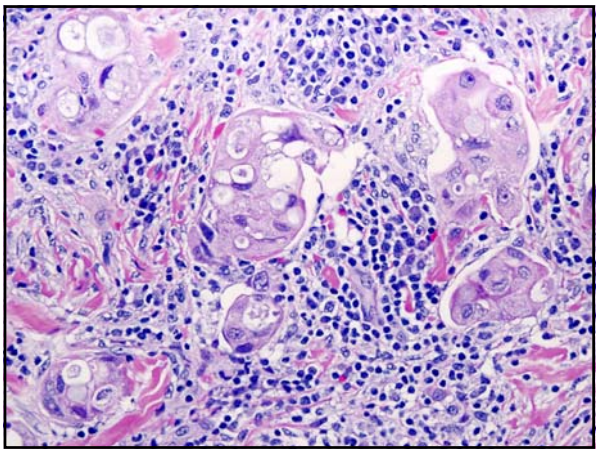
Pathologic Examination After NACT

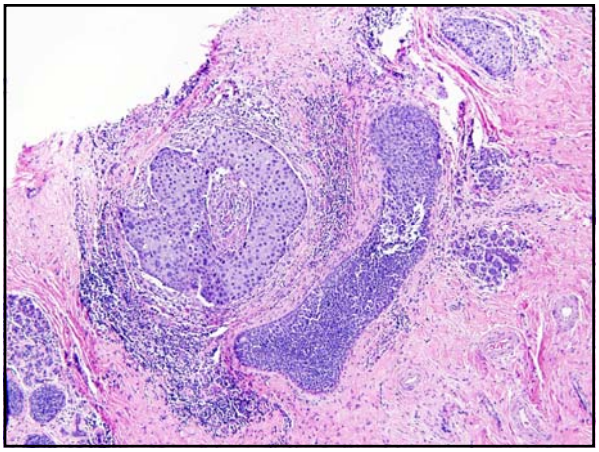
- Microscopic examination
  - **Residual invasive carcinoma**
    - **Most do not show change in morphology, some do**
    - **Some may show marked retraction artifact**
    - **Tumor in lymphovascular spaces are resistant to therapy**
    - **Immunohistochemical stains for pancytokeratin and myoepithelial markers may be helpful**

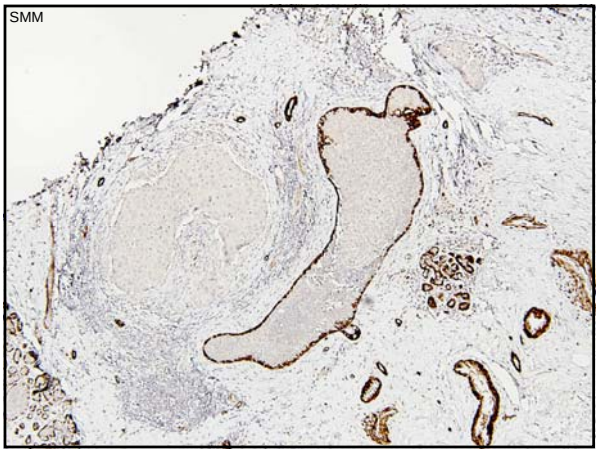








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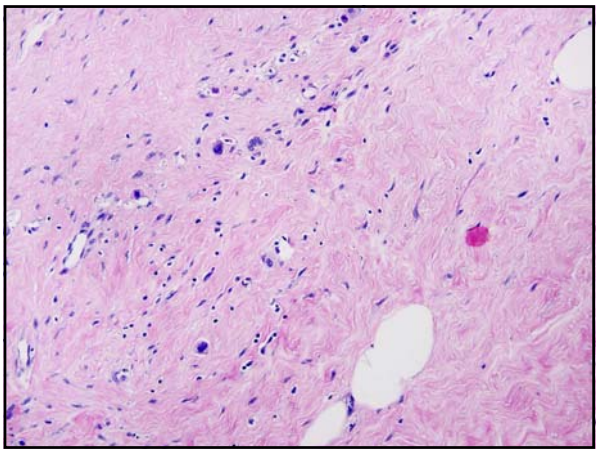

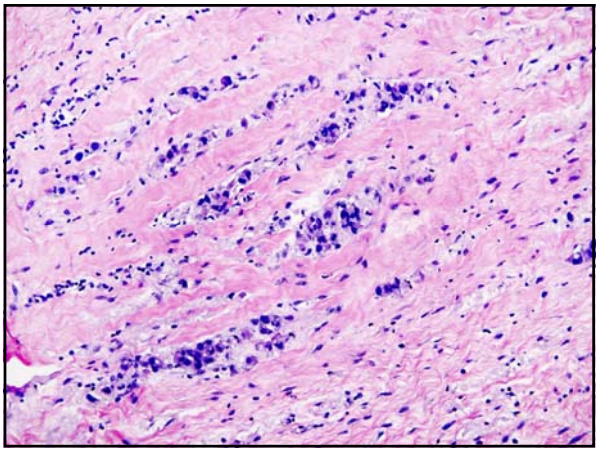

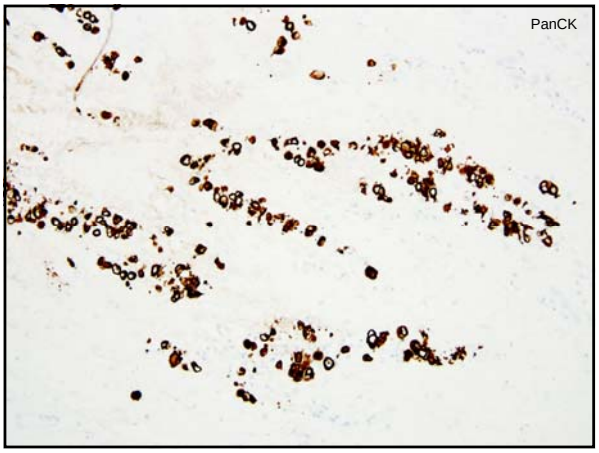
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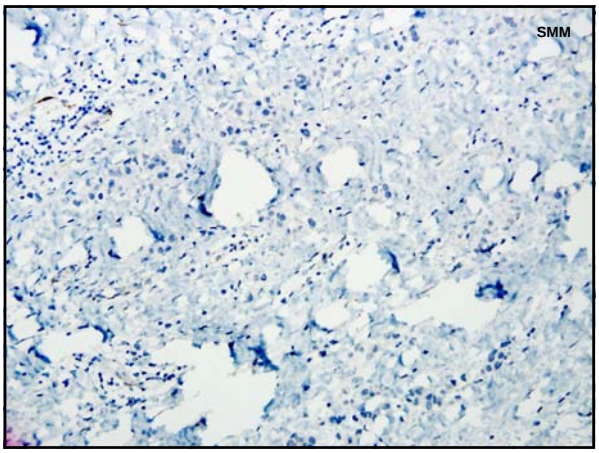
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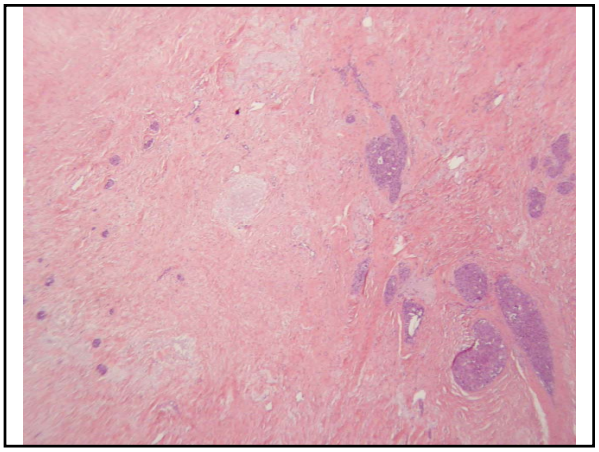

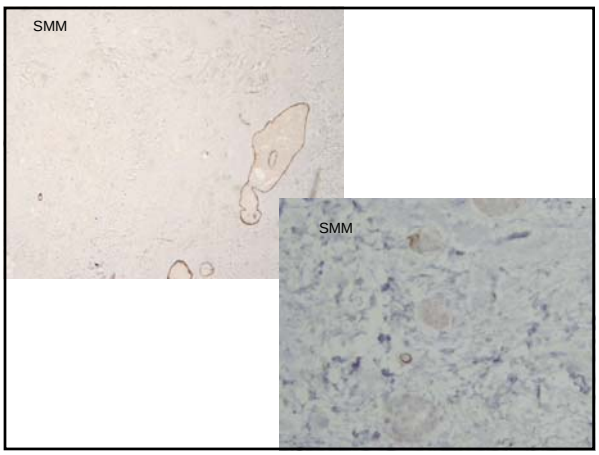
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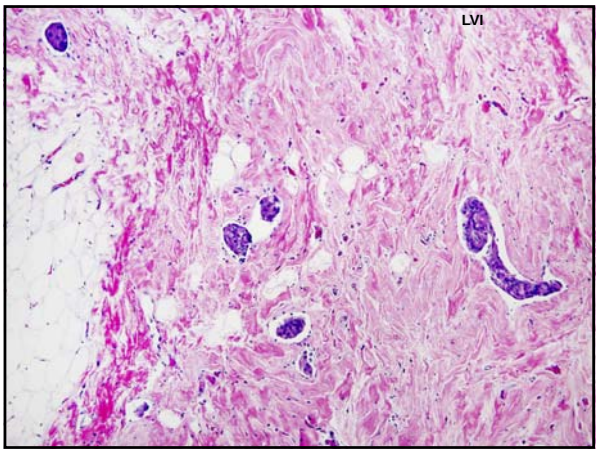
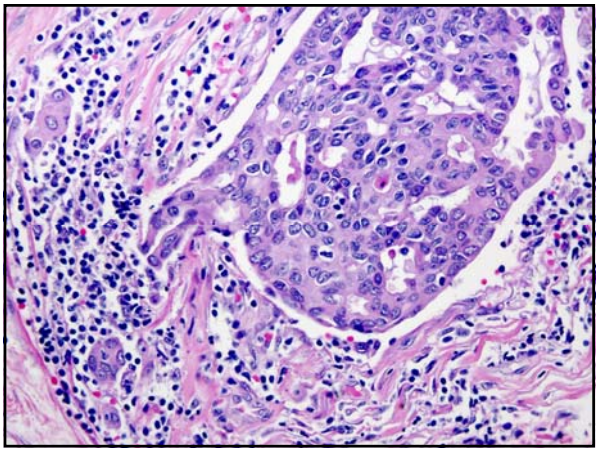
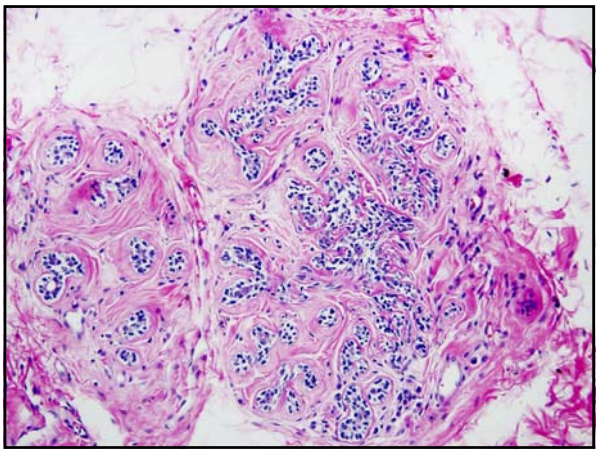
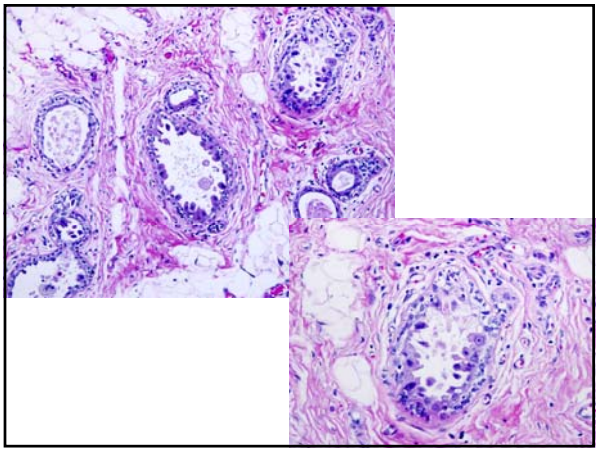




Pathologic Examination After NACT

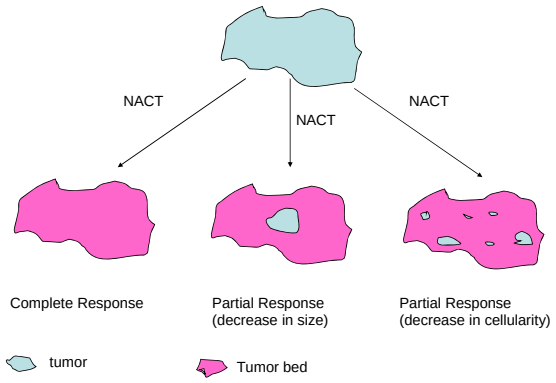
- Microscopic examination
  - **Changes in normal breast tissue**
    - **Hyalinization of intralobular stroma and basement membrane**
    - **Cells may show enlargement, hyperchromasia and nuclear smudging**





Pathologic Examination After NACT

- Microscopic examination
  - **Residual tumor size**
  - **Residual tumor cellularity**
  - **Tumor margins**
  - **Tumor grade**
  - **Tumor markers**



Pathologic Examination After NACT

- Microscopic examination
  - **Residual tumor size**
    - **Single largest contiguous focus**
    - **Multiple foci**
      - Multiple areas of invasive carcinoma over a 4 cm fibrotic tumor bed area, the largest measuring 1.5 cm

Pathologic Examination After NACT

- Microscopic examination
  - **Residual tumor cellularity**
    - **The change in cellularity may be more important than the change in size.**
    - **Cellularity is assessed by estimating the percentage area of the overall tumor bed comprised of invasive carcinoma.**

Table 1. Criteria Used in Different Systems for Categorizing Response to Treatment*

NSABP B-18[7]	
Category	
pCR	No recognizable invasive tumor cells present
pPR	The presence of scattered individual or small clusters of tumor cells in a desmoplastic or hyaline stroma
pNR	Tumors not exhibiting the changes listed above
Miller-Payne System[10]	
Grade 1	No change or some alteration to individual malignant cells, but no reduction in overall cellularity (pNR)
Grade 2	A minor loss of tumor cells, but overall cellularity still high; up to 30% loss (pPR)
Grade 3	Between an estimated 30% and 90% reduction in tumor cells (pPR)
Grade 4	A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; >90% loss of tumor cells (almost pCR)
Grade 5	No malignant cells identifiable in sections from the site of the tumor; only vascular fibroelastotic stroma remains, often containing macrophages; however, ductal carcinoma in situ may be present (pCR)
Chevallier Method[9]	
Class 1	Disappearance of all tumor (pCR)
Class 2	Presence of DCIS in the breast, no invasive carcinoma and negative lymph node (pCR)
Class 3	Presence of invasive carcinoma with stromal alteration (pPR)
Class 4	Few modifications of the tumoral appearance (pNR)

Sataloff Method[8]	
Tumor	
T-A	Total or near total therapeutic effect (pCR)
T-B	>50% therapeutic effect, but less than total or near total (pPR)
T-C	<50% therapeutic effect, but effect evident (pPR)
T-D	No therapeutic effect (pNR)
Nodes	
N-A	Evidence of therapeutic effect, no metastatic disease
N-B	No nodal metastasis or therapeutic effect
N-C	Evidence of therapeutic effect, but nodal metastasis present
N-D	Viable metastatic disease, no therapeutic effect
RCB System[11]	
RCB-0	No carcinoma in breast or lymph node (pCR)
RCB-I	Partial response
RCB-II	Partial response
RCB-III	Chemoresistant
AJCC "y" Classification[12]	
Category	
T	Uses same criteria as before treatment
N	Uses same criteria as before treatment

* NSABP indicates National Surgical Adjuvant Breast and Bowel Project; pCR, pathologic complete response; pPR, pathologic partial response; pNR, pathologic no response; DCIS, ductal carcinoma in situ; RCB, residual cancer burden; and AJCC, American Joint Committee on Cancer.

Sahoo S, Lester SC. Arch Pathol Lab Med 2009; 133: 633-642

- The AJCC system
  - **Use the prefix "y" (ypTNM)**
  - **If multiple nests of residual tumors, the extent that encompasses these tumor nests is used for the T staging**
  - **Does not include changes in cellularity in the system**

Carey LA, Metzger R, et al. J Natl Cancer Inst. 2005; 97: 1137-1142

- The Miller-Payne system
  - **Uses tumor cellularity to divide tumors into five grades**
    - 1-no reduction in overall cellularity
    - 2-up to 30% loss
    - 3-between 30-90% reduction in tumor cels
    - 4-more than 90% loss
    - 5-no residual tumor. DCIS may be present
  - **Grades correlated with overall survival and disease free survival**
  - **Identification of small foci of residual invasive carcinoma is important**
  - **Lymph node is not included in this system**

Ogston KN, Miller ID, Payne S, et al. Breast 2003; 12: 320-327.

- RCB system
  - **Using the following parameters**
    - Primary tumor bed size
    - Residual cancer cellularity
    - Percentage of cancer that is DCIS
    - Number of positive lymph nodes
    - Diameter of largest metastasis
  - **RCB**
    - 0-No carcinoma in breast or lymph node (pCR)
    - I-Partial response
    - II-Partial response
    - III-Chemoresistant

www.mdanderson.org/breastcancer_RCB

Symmans WF, Peintinger F, et al. J Clin Oncol 2007; 25: 4414-4422.

Pathologic Examination After NACT

- Microscopic examination
  - *Residual tumor size*
  - *Residual tumor cellularity*
  - Tumor margins
    - Correlate the gross and microscopic measurements
    - The significance of tumor bed at the margin is unclear in patients with pCR
  - Tumor grade
    - If there is insufficient residual tumor for histologic grading, give nuclear grade
  - Tumor markers
    - ER/PR/Her-2- usually the same, but not always.
    - Oncologists always request them to be repeated.

Reporting After NACT

- Pathology report should include:
  - Presence and size of tumor bed
  - Extent and cellularity of residual invasive cancer
  - Nuclear and histological grade of residual cancer
  - LVI
  - Presence and extent of DCIS
  - Margins with respect to tumor bed, invasive and in-situ carcinoma
  - Evidence of treatment-induced effects
  - Additional immunohistochemical studies, including prognostic markers
  - A comment of the overall response to treatment

Examination of Lymph Nodes after NACT

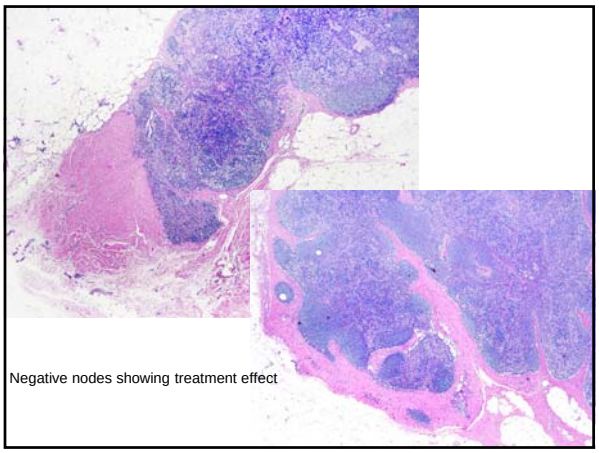
- Patients who have clinically negative axillary nodes prior to NACT undergo sentinel lymph node biopsy at the time of the primary breast surgery.
- Patients who have a positive axillary node diagnosed by core needle biopsy prior to NACT usually undergo complete axillary node dissection at the time of the primary breast surgery.

Examination of Lymph Nodes after NACT

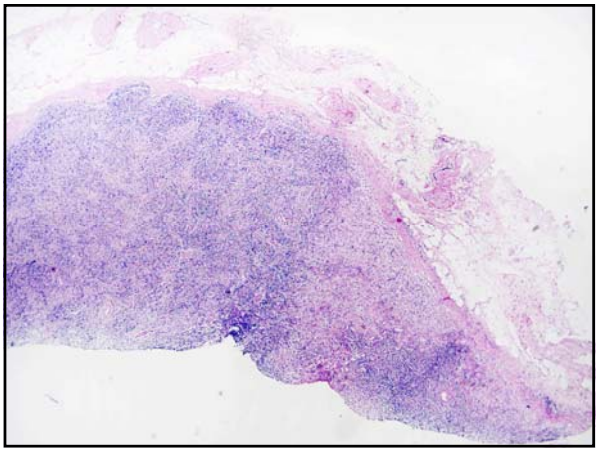
- Gross Examination
  - Lymph nodes may be difficult to recognize due to atrophy and fibrosis after NACT.
  - Submit all fibrotic areas in the fat and around the vessels.

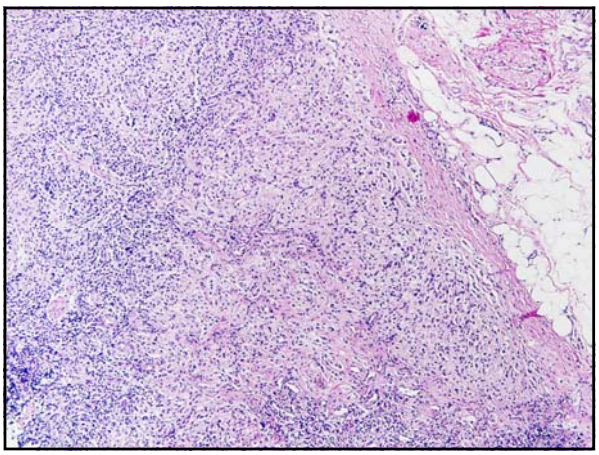
Examination of Lymph Nodes after NACT

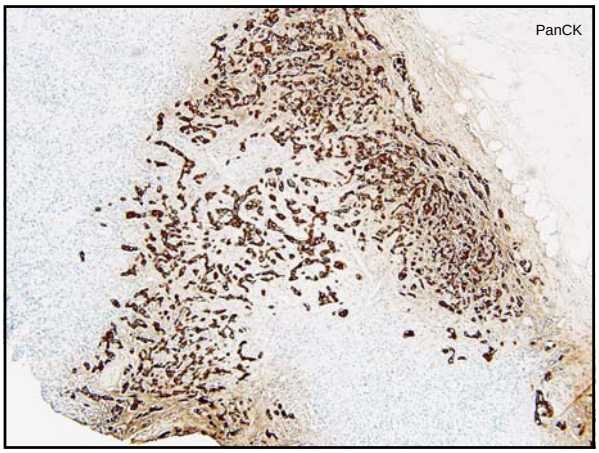
- Microscopic Examination
  - Positive node without treatment effect
  - Positive node with treatment effect
    - Better disease-free survival and lower relapse rates
  - Negative node with treatment effect
    - Indicating a complete response
  - Negative node without treatment effect

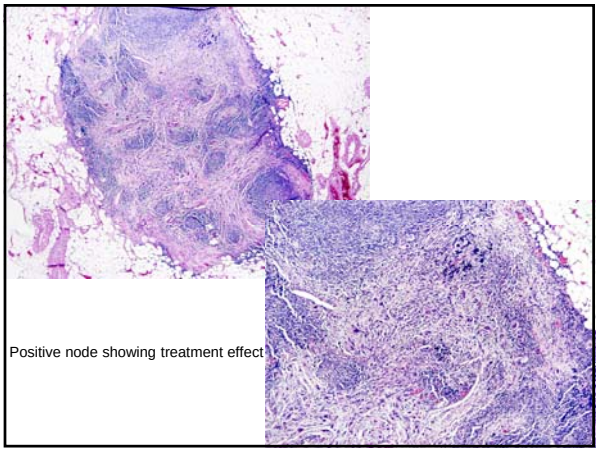


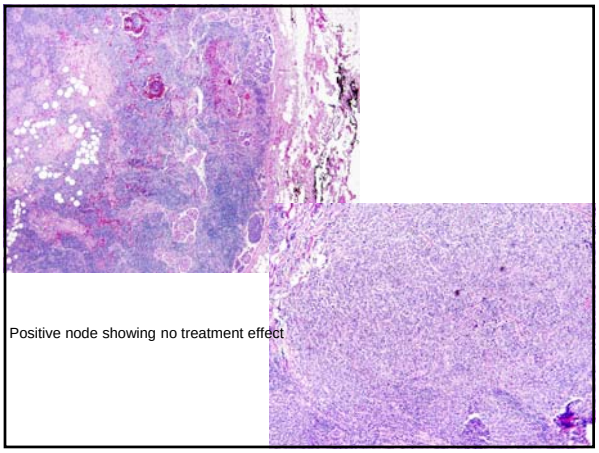
Negative nodes showing treatment effect

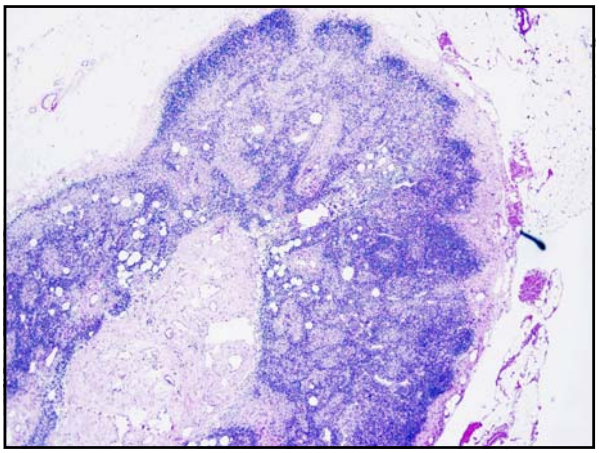


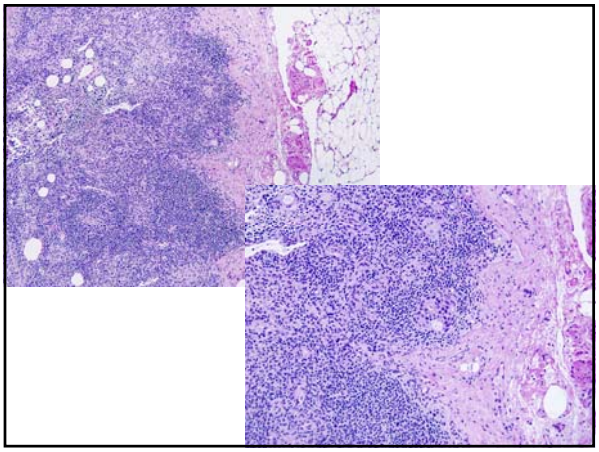


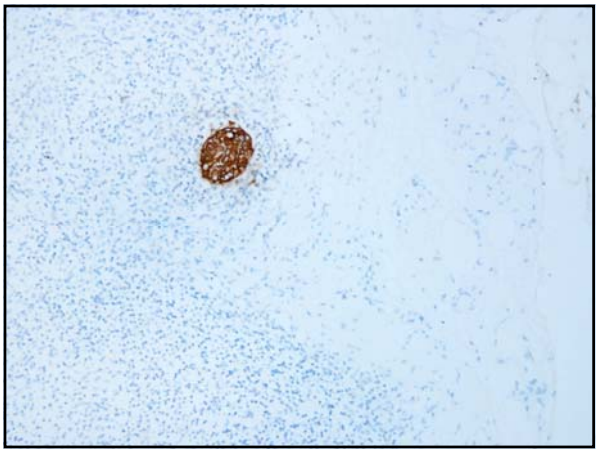

PanCK


Positive node showing treatment effect


Positive node showing no treatment effect







Examination of Lymph Nodes after NACT

- Microscopic Examination
  - Treatment effect
    - Hyaline stromal scars, mucin pools, aggregates of histiocytes
  - Size of the largest metastasis
    - The prognostic significance of ITCs and micromets, especially in a background of treatment effect, is different from those without NACT
  - Presence of extracapsular extension (ECE)

Reporting of Lymph Nodes

- Number of lymph nodes
- Number of lymph nodes with metastases
  - Size of the largest metastasis
  - Presence of ECE
- Number of lymph nodes with metastases showing treatment effect
- Number of negative lymph nodes showing treatment effect

INVASIVE CARCINOMA OF THE BREAST STATUS POST NEOADJUVANT THERAPY

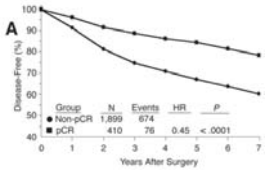
CHECKLIST:

Specimen Type:
Laterality:
Tumor Site:
Tumor Bed Identified: Yes/No
Size/Extent of Tumor Bed:
Size/Extent of Residual Invasive Tumor:
Overall Residual Viable Cancer Cellularity of the Tumor Bed: %
Ductal Carcinoma In-situ (DCIS):
Present/Absent, % in the residual carcinoma (if present)
Histologic Type:
Histologic Grade (Nottingham Histologic Score):
Tubule Formation:
Nuclear Grade:
Mitotic Count (40x objective):
Total Nottingham Score: /9
Surgical Margins: **Please indicate the distance
Lymph-Vascular Invasion:
Perineural Invasion:
Nipple Involvement:
Skin Involvement:

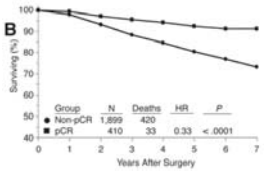
Lymph Node Sampling:
No lymph node sampling
Sentinel lymph node(s) only
Sentinel lymph node with axillary dissection
Axillary dissection
Total number of involved nodes/total nodes found
Size of largest metastasis: _____ cm
Extranodal extension:
Non-neoplastic Breast Tissue:
Overall Response to Neoadjuvant Therapy:
In the Breast: No/Minimal/Partial/Complete
In the Lymph Nodes: **No/Minimal/Partial/Complete**
Prognostic markers:
Time between tumor removal and placement into formalin < 1 hour: Yes/No
Fixation Time between 6-48 hours: Yes/No
Pathologic Staging:
ypT___ N___ M___

Pathologic Complete Response to Neoadjuvant Chemotherapy Is Correlated with Improved Disease-free and Overall Survival (NSABP B-27)

Disease-free survival



Overall survival



- **There was no significant difference in overall survival (OS) between the treatment arms (data not shown).**
- **Pathologic CR (pCR) was a significant predictor of OS, regardless of treatment.**
- ***How can we identify the patients most likely to have pCR to neoadjuvant chemotherapy?***

Bear H D, et al. *J Clin Oncol*. 2006;24(13):2019-2027.

Predictive Factors for Response to NACT

- Factors associated with a favorable response
  - High nuclear grade
  - ER negativity
  - High mitotic index
  - Tumor necrosis
- Factors associated with an unfavorable response
  - ER positivity
  - Well-differentiated tumor
  - Her-2 overexpression
- Molecular/genomic predictors

Buchholz TA, Hunt KK, et al. Cancer 2003; 98: 1150-1160
Pu RT, Schott AF, et al. AM J Surg Path 2005;29:354-8
Rouzier R, Perou CM, et al. Clin Ca Res 2005;11:5678-85.
Tabchy A, Valero V, et al. Clin Cancer Res 2010; 16:5351-61.

Conclusions

- Neoadjuvant chemotherapy will be used more frequently in a wider range of patients.
- Pathologists play a critical role in evaluating tumor response.
- A better classification of partial response in the breast and nodes is needed.
- Research studies using pre- and post-treatment specimens may help in the understanding of mechanisms of tumor response and tailor effective treatment for individual patient.

Testicular Tumors=90% Tumors

- 90% in the age group 25-45 years
- 90% of germ cell origin
- 90% malignant
- 90% curable by modern treatment modalities ---surgical-chemotherapy

Testicular Tumors

- T Teratoma
- E Embryonal carcinoma
- S Seminoma
- T Tertocarcinoma
- I Intratubular testicular germ cell neoplasia
- C Choriocarcinoma
- L Leydig cell tumor
- E Endodermal sinus tumor (yolk sac tumor)
- S Sertoli cell tumor

Testicular Germ Cell Tumors

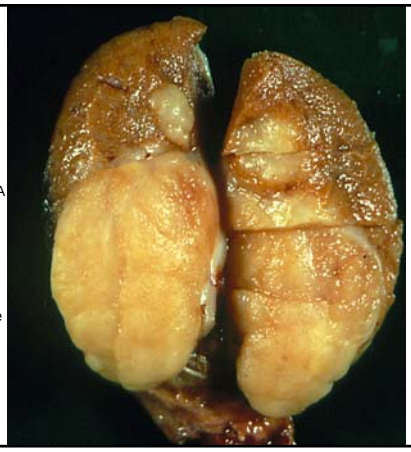
- Simplified Classification(90% of tumors)
  - Seminoma
    - More sensitive to radiation and chemotherapy
  - Non-seminomatous germ cell tumors (NSGCT)
    - Embryonal carcinomas
    - Yolk sac tumors
    - Choriocarcinomas
    - Teratomas
  - Mixed germ cell tumor (seminoma+NSGCT)

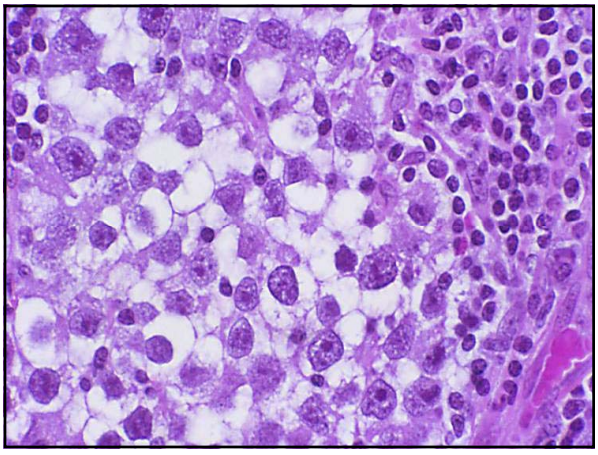
It was not always like that!

- Patton JF, Hewett CB, Mallis N: Diagnosis and treatment of tumors of the testis. JAMA 1959; 171: 2194-2198.

Tumor	Survival	Survival Surgery (RPLND)	
	Radiother.	Nodes(+)	(-)
Seminoma	87%	--	--
Embryonal ca.	13%	65%	76%
Teratocarcinoma	18%	30	74%

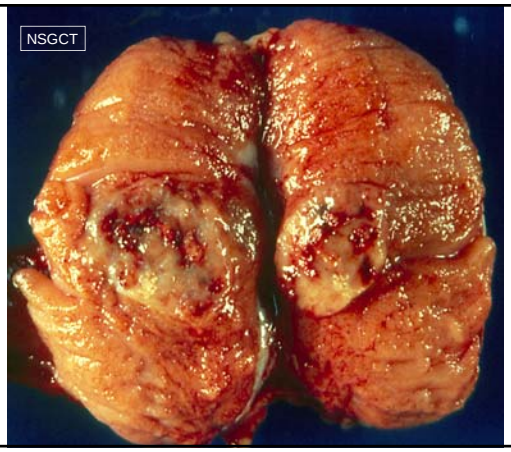
SEMINOMA
AFP –
hCG –
=======
Note: May contain trophoblast and secrete small amounts of hCG

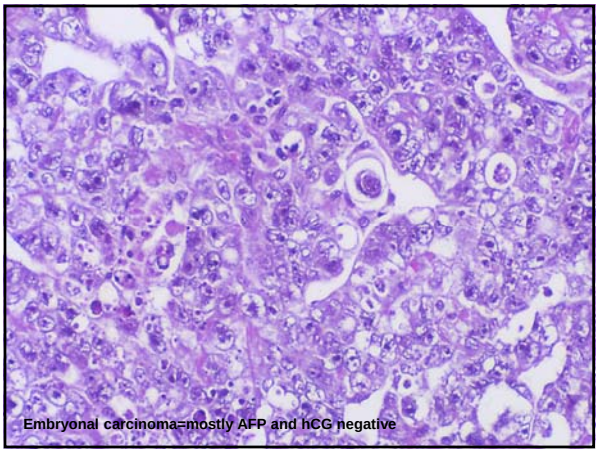




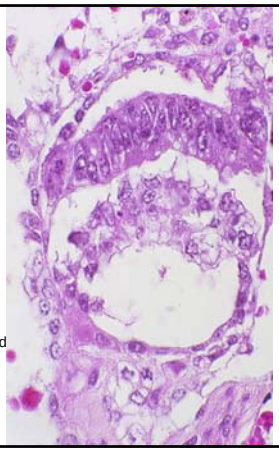
Nonseminomatous germ cell tumors

- Embryonal carcinoma
- Teratocarcinoma (malignant mixed germ cell tumor)
- Choriocarcinoma
- Yolk sac carcinoma
- Teratoma





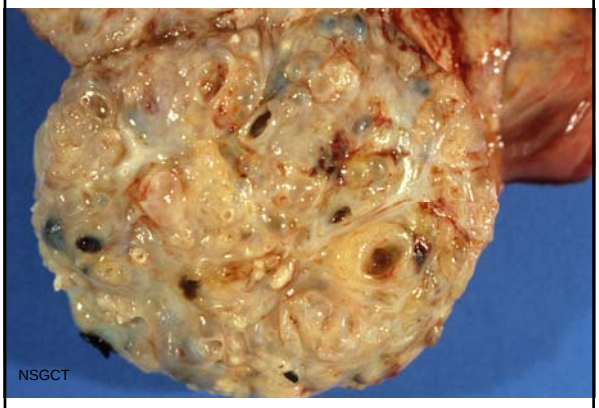
Embryoid body composed of ECC and primitive endoderm



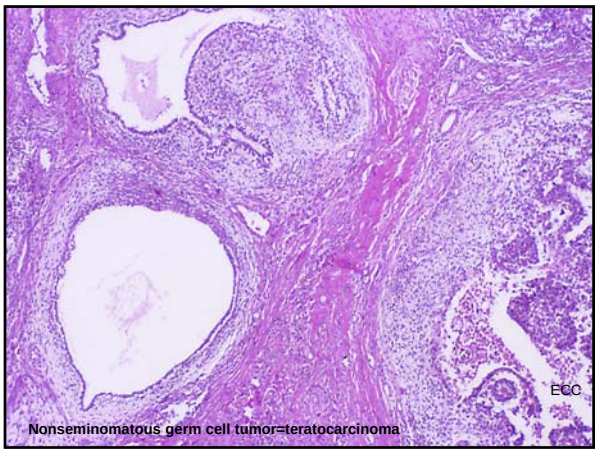
If tumor composed of Embryoid bodies= "polyembryoma"

Embryonal Carcinoma

- EC is a cell type
- EC is tumor type
- EC can show several histologic patterns
- EC can be the stem cell of NSGCT
- EC can differentiate into non-proliferating somatic cells and usually lose its malignancy
- EC metastasize



NSGCT



Nonseminomatous germ cell tumor=teratocarcinoma

Teratocarcinoma

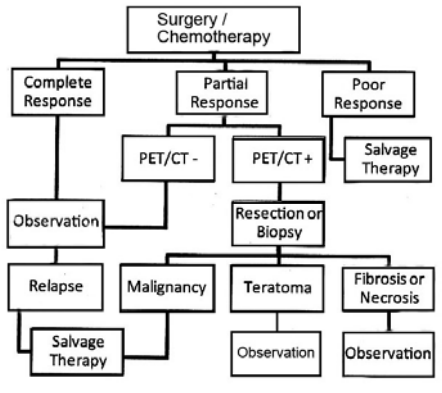
- Malignant tumor
- EC are stem cells imparting malignancy
- Somatic tissues are “benign”
- Extraembryonic tissues (yolk sac and trophoblastic cells) can be benign or malignant
- Secondary malignancy - YSC, choriocarcinoma mediastinal TC with leukemia

Testicular Germ Cell Tumors

- Prognostic factors
  - Tumor type
  - Tumor Stage
  - Serum markers
    - hCG
    - AFP
    - LDH
  - Nonpulmonary visceral metastases

Testicular Germ Cell Tumors

- Treatment Options
  - Seminoma
    - Orchiectomy + surveillance or radiation therapy
    - Chemotherapy
  - Non-seminomatous germ cell tumors (NSGCT)
    - Orchiectomy
    - Chemotherapy
    - Surgical removal of residual masses (retroperitoneal lymph node dissection, RPLND)



Adapted from *Wieder Pocket Guide to Urology*

Testicular Germ Cell Tumors

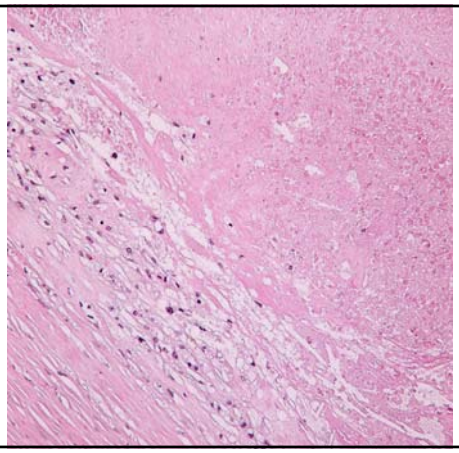
- Surgical resection of residual masses after post-orchiectomy chemotherapy-clinical decision, including tumor markers (AFP, hCG)
  - There are no definite predictors of the histology of residual masses besides HISTOLOGY
  - The presence of persistent nonseminomatous germ-cell malignant elements in the resected specimen is a poor prognostic indicator and an indication for additional chemotherapy

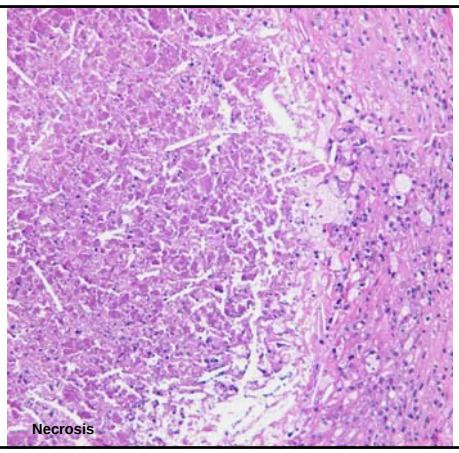
Specimen Sampling

- Post chemotherapy RPLND specimen
  - Submit all identifiable lymph nodes
  - For large masses that have obliterated individual lymph nodes, take 1 section for every centimeter of the largest dimension of the mass (Per CAP checklist)
  - It's important to sample different looking areas
  - Would submit all if no residual tumor is seen in the initial sections

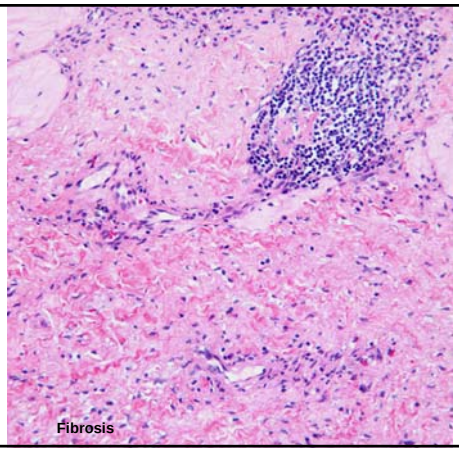
Microscopic Examination

- Post chemotherapy RPLND specimen
  - Necrosis
  - Fibrosis
  - Persistent tumor
    - Teratoma
    - Non-teratomatous germ cell tumor (e.g., yolk sac carcinoma)
    - "somatic-type" malignancy-rhabdomyosarcoma msot common

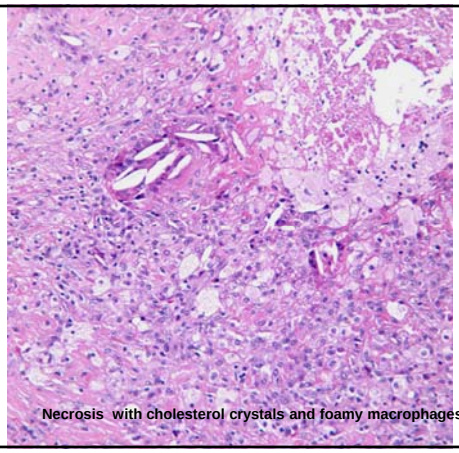




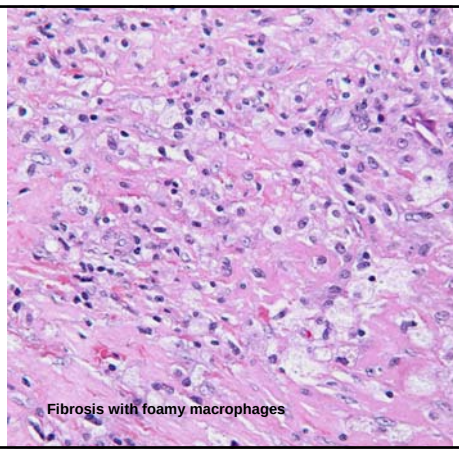
Necrosis



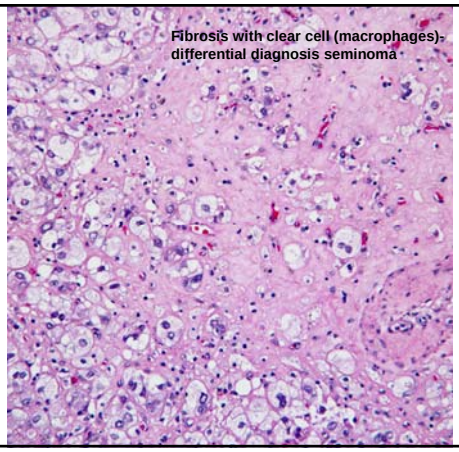
Fibrosis



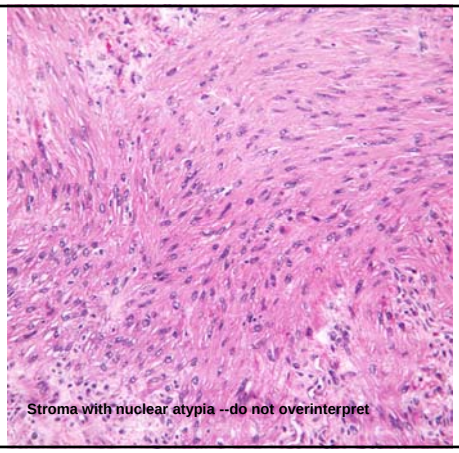
Necrosis with cholesterol crystals and foamy macrophages



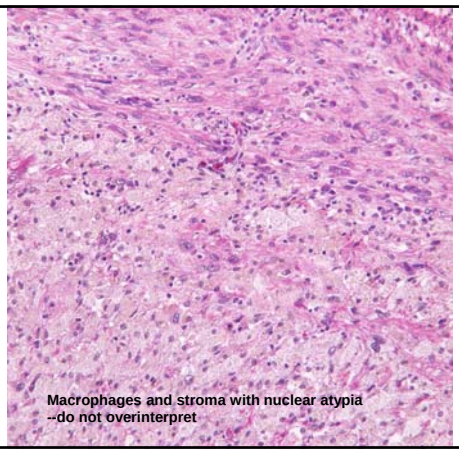
Fibrosis with foamy macrophages



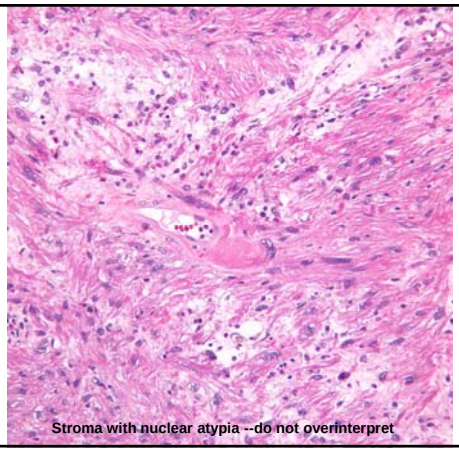
Fibrosis with clear cell (macrophages), differential diagnosis seminoma



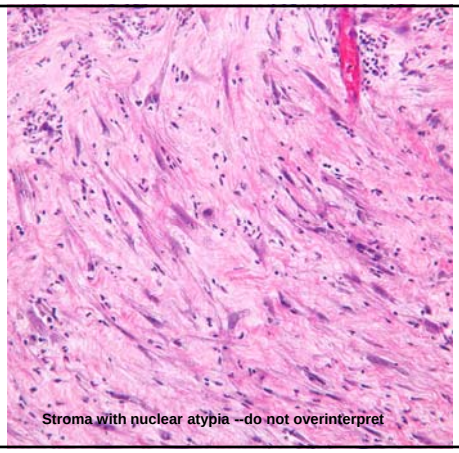
Stroma with nuclear atypia --do not overinterpret



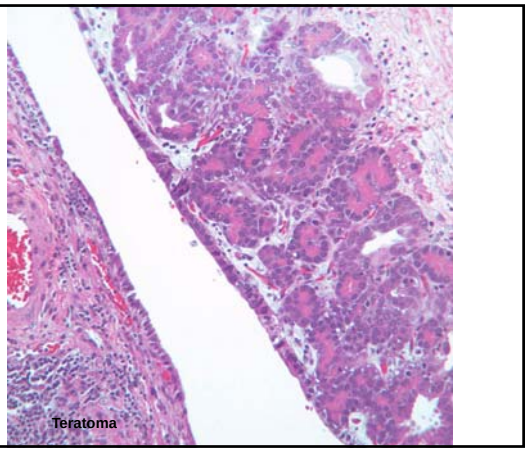
Macrophages and stroma with nuclear atypia --do not overinterpret

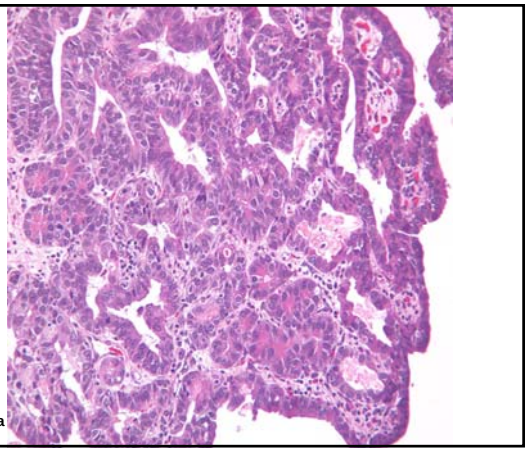


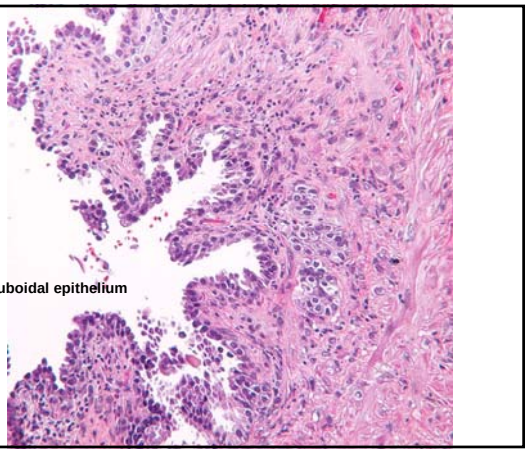
Stroma with nuclear atypia --do not overinterpret

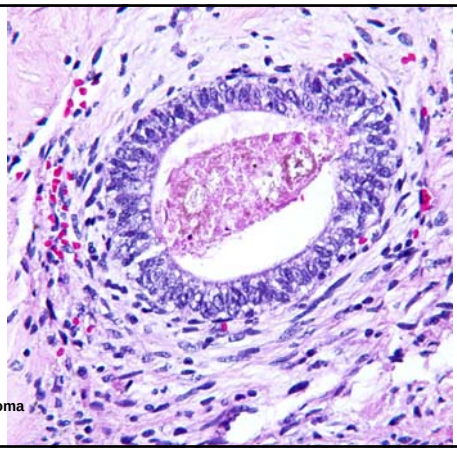


Stroma with nuclear atypia --do not overinterpret

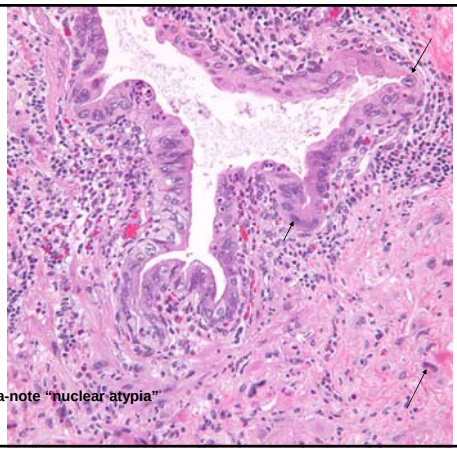

Teratoma


Teratoma

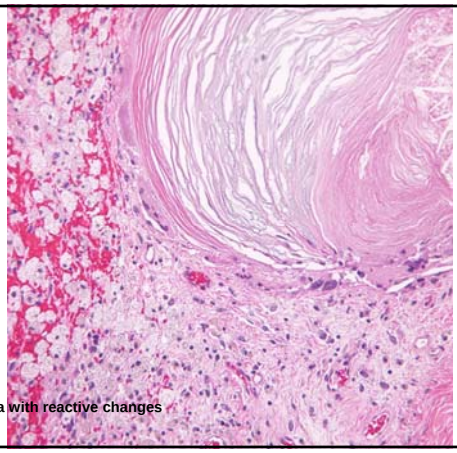

Ductal cuboidal epithelium



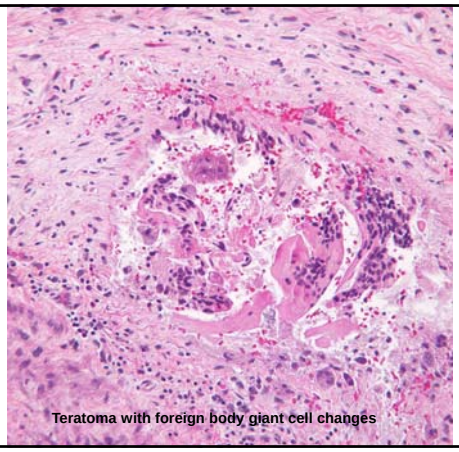
Teratoma



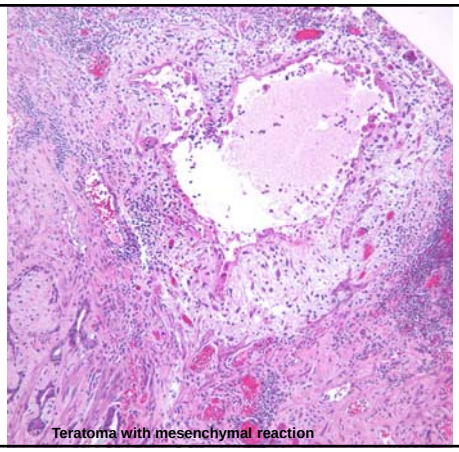
Teratoma-note “nuclear atypia”



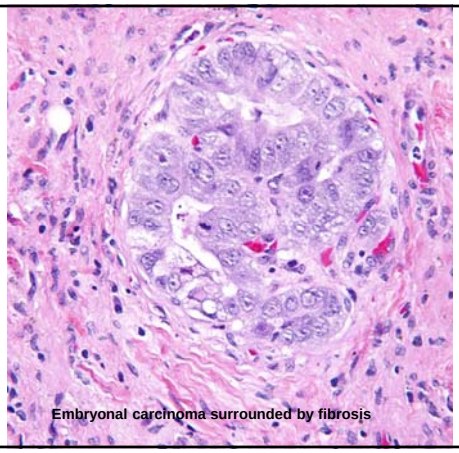
Teratoma with reactive changes



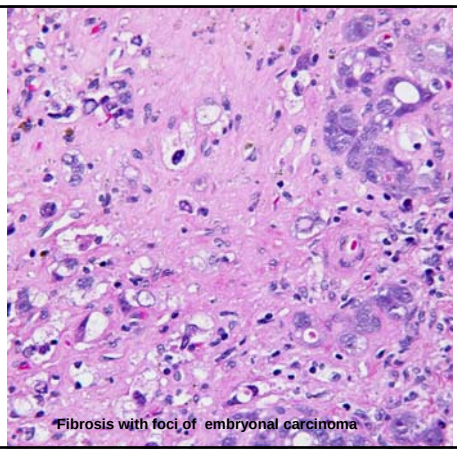
Teratoma with foreign body giant cell changes



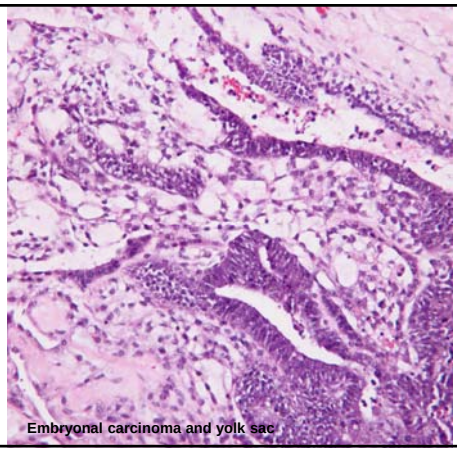
Teratoma with mesenchymal reaction



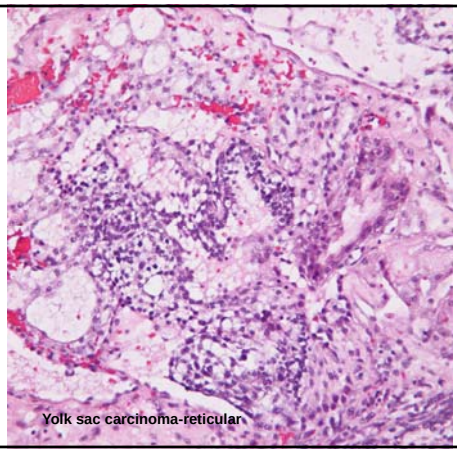
Embryonal carcinoma surrounded by fibrosis



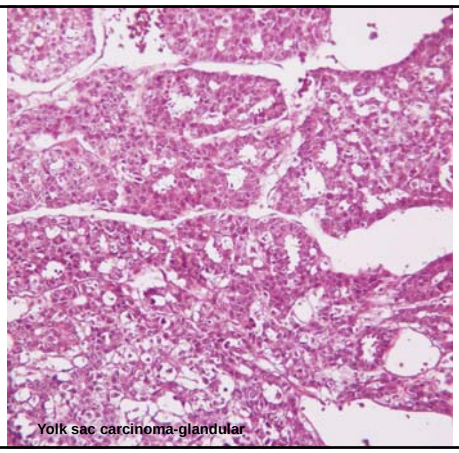
Fibrosis with foci of embryonal carcinoma



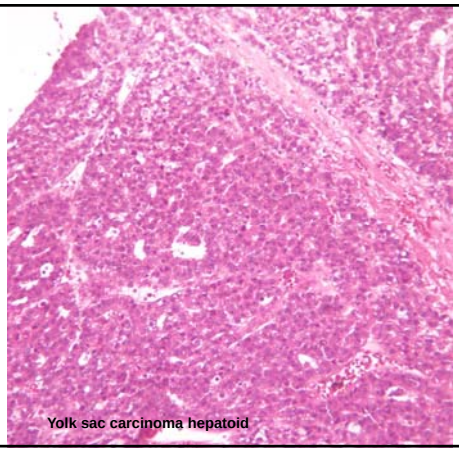
Embryonal carcinoma and yolk sac



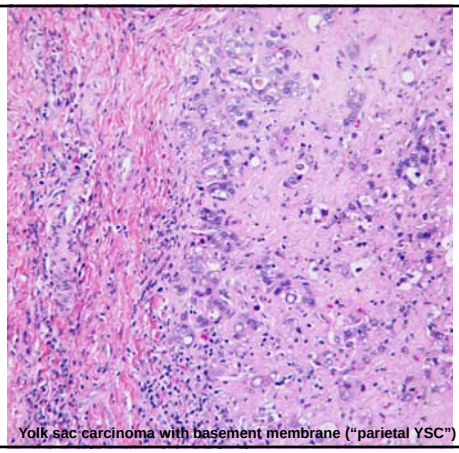
Yolk sac carcinoma-reticular



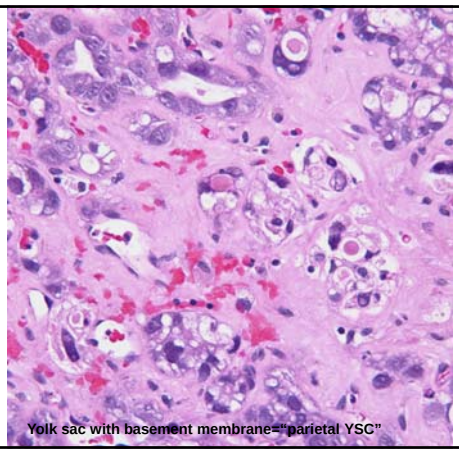
Yolk sac carcinoma-glandular



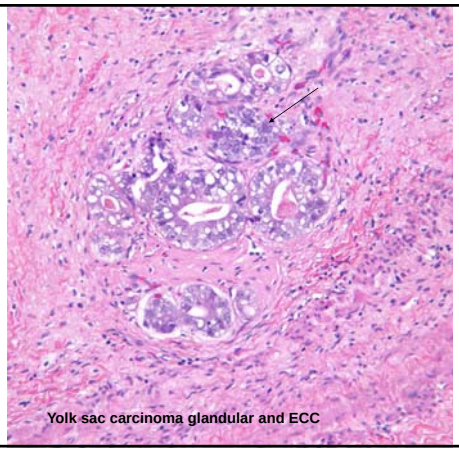
Yolk sac carcinoma hepatoid



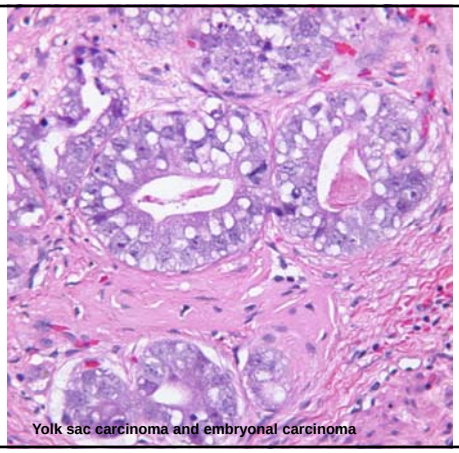
Yolk sac carcinoma with basement membrane ("parietal YSC")



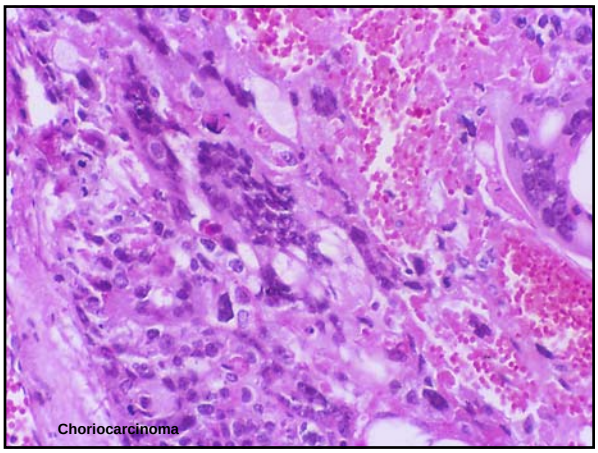
Yolk sac with basement membrane="parietal YSC"



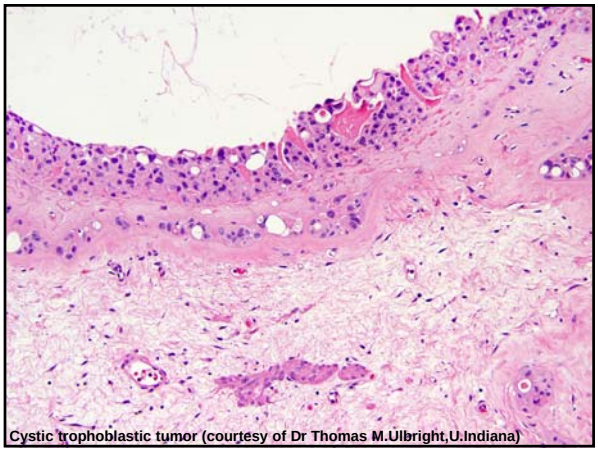
Yolk sac carcinoma glandular and ECC



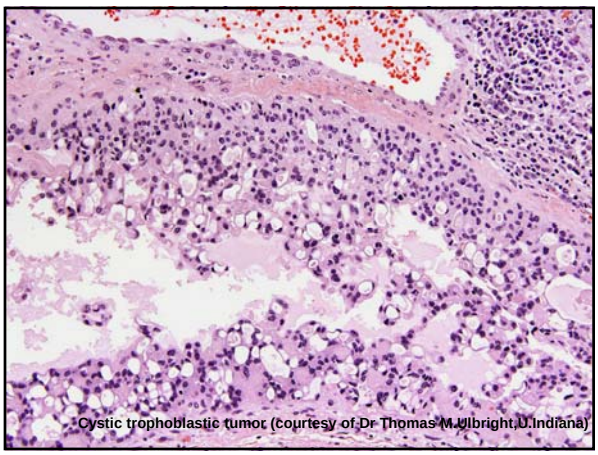
Yolk sac carcinoma and embryonal carcinoma



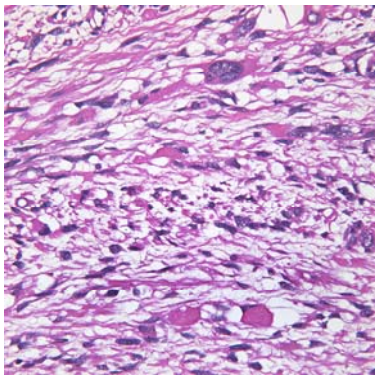
Choriocarcinoma



Cystic trophoblastic tumor (courtesy of Dr Thomas M.Ulbright,U.Indiana)



Cystic trophoblastic tumor (courtesy of Dr Thomas M.Ulbright,U.Indiana)



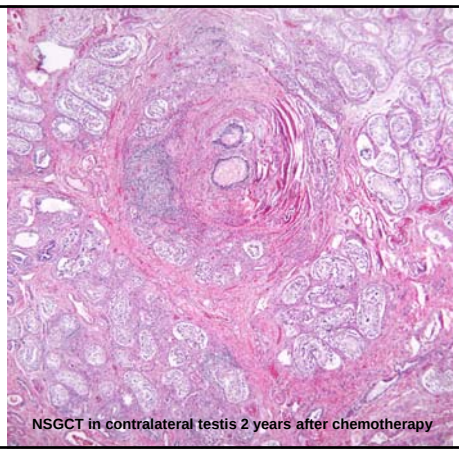
Rhabdomyosarcoma—the most common non-germ cell malignancy

Non-germ Cell Malignancies After Chromotherapy of NSGCT

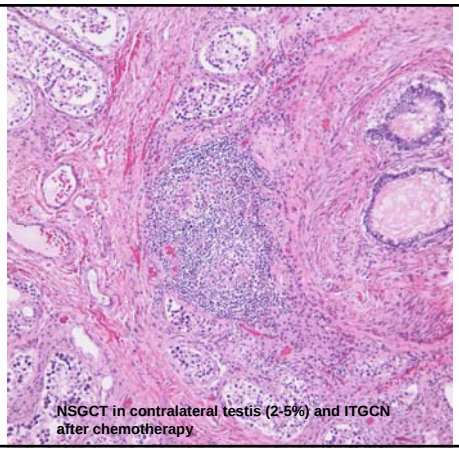
- Rare-important--resistant to chemotherapy
- Show “somatic cell phenotype”
- Sarcomas more common than carcinoma
- Rhabdomyosarcoma the most common
- Other sarcomas, adenocarcinomas
- Uncommon but reported: PNET, nephroblastoma

Contralateral Testis

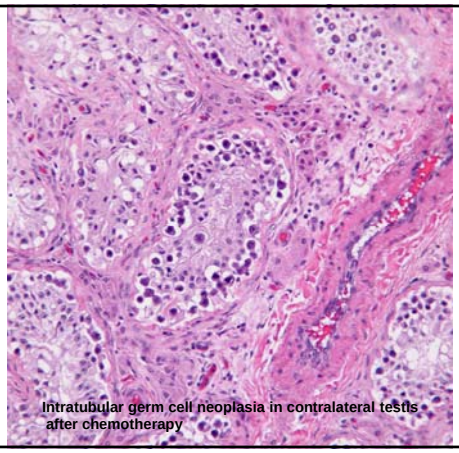
- Malignancy in 2-5% of cases
- Synchronous or metachronous
- Vast majority within 5 years of orchiectomy
- Usually same type of tumor
- 90% are seminomas



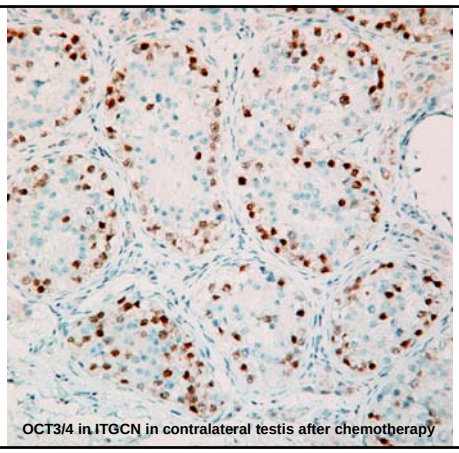
NSGCT in contralateral testis 2 years after chemotherapy



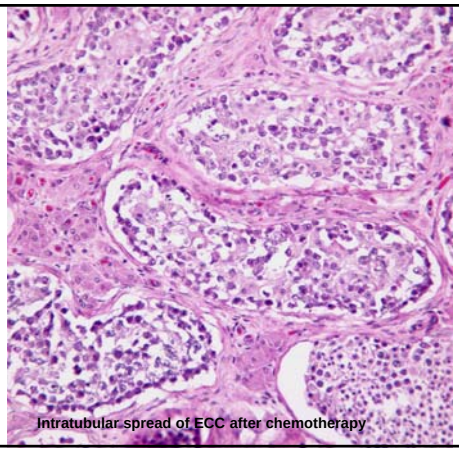
NSGCT in contralateral testis (2-5%) and ITGCN after chemotherapy



Intratubular germ cell neoplasia in contralateral testis after chemotherapy



OCT3/4 in ITGCN in contralateral testis after chemotherapy



Intratubular spread of ECC after chemotherapy

Learning Points

- Post chemotherapy RPLND specimen
  - Necrosis
    - Pyknotic nuclei and ghost tumor cell nuclei do not count as persistent tumor cells
    - Do not misinterpret reactive histiocytes with clear cytoplasm and prominent nucleoli as residual tumor, especially if the primary was a seminoma!!
    - Multiple sections to be examined –look for residual embryonal carcinoma

Learning Points

- Post chemotherapy RPLND specimen
  - Fibrosis
    - WATCH for residual EC cells
    - Hyalinized areas with glandular atypical cells—watch out for YOLK SAC CARCINOMA (“parietal”)
    - Spindle to stellate cells, may show cytologic atypia and pleomorphism
    - Probably represent the stroma of the germ-cell tumor (“stroma exclusive teratoma”)
    - Be careful not to miss a real sarcoma=rare

Learning Points

- Post chemotherapy RPLND specimen
  - Persistent tumor
    - Teratoma
      - Diagnosis “metastatic teratoma”—the urologist know what you mean=benign, do not over interpret!
      - May show atypical cytologic features, especially in glands and cartilage but if it shows “somatic differentiation”, do not worry
      - Avoid using mature or immature teratoma in this setting, not to confuse your urologists
      - Make sure there are no EC or YSC elements!!
      - SIZE MATTERS—25% of postchemotherapy “benign” teratomas >> 10 cm will recur!

Learning Points

- Post chemotherapy RPLND specimen
  - Persistent tumor
    - Seminoma—metastasize as seminoma
    - NSGCT usually metastasize as embryonal carcinoma which may form YSC or choriocarcinoma
    - Serologic markers important for follow up!!
    - Metastases that contain malignant components of NSGCT most often ECC, but may be YSC or choriocarcinoma
    - Note -cystic trophoblastic tumor is benign (rare finding)!
    - Secondary non-germ cell malignancy rare but resistant to chemotherapy.
      - Sarcoma>adenocarcinoma>PNET>nephroblastoma

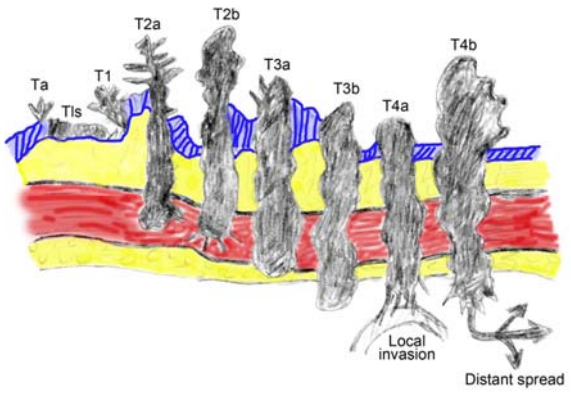
Clinical Implication

- Post chemotherapy RPLND specimen
  - Necrosis
  - Fibrosis
  - Persistent tumor

  No further treatment needed
  Clinical surveillance
    - Teratoma
    - Non-teratomatous germ cell tumor –**Need additional chemotherapy**
    - Somatic malignancy ("non germ cell tumor") – **resistant to chemotherapy, poor prognosis**

Urinary Bladder

- Introduction
- Case presentations



Urinary Bladder

- Stage 0 (Ta/Tis, N0, M0) and Stage 1 (T1,N0,M0)
  - Transurethral resection (TUR) with fulguration
  - Followed by intravesical BCG or intravesical chemotherapy

Urinary Bladder

- Stage II, stage III and some stage IV (T2-T4aN0-N2M0)
  - Radical cystectomy with adjuvant or neoadjuvant chemotherapy

Cancer, 2011,DOI: 10.1002/cncr.26278

A Comparison of the Outcomes of Neoadjuvant and Adjuvant Chemotherapy for Clinical T2-T4aN0-N2M0 Bladder Cancer

Matthew S. Wosnitzer, MD[1]; Gregory W. Hruby, BA[1]; Alana M. Murphy, MD[1]; Lamont J. Barlow, MD[1]; Carlos Cordon-Cardo, MD, PhD[2]; Mahesh Mansukhani, MD[2]; Daniel P. Petrylak, MD[3]; Mitchell C. Benson, MD[1]; and James M. McKiernan, MD[1]

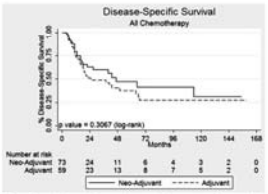


Figure 2. Kaplan-Meier estimated disease-specific survival (DSS) is shown for patients treated with neoadjuvant chemotherapy versus adjuvant chemotherapy. No statistically significant difference was identified in DSS between the neoadjuvant and adjuvant systemic chemotherapy groups.

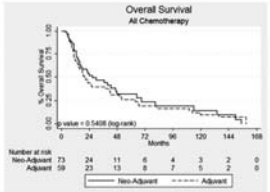


Figure 3. Kaplan-Meier estimated overall survival (OS) is shown for patients treated with neoadjuvant chemotherapy versus adjuvant chemotherapy. No statistically significant difference was identified in OS between the neoadjuvant and adjuvant systemic chemotherapy groups.

Urinary Bladder

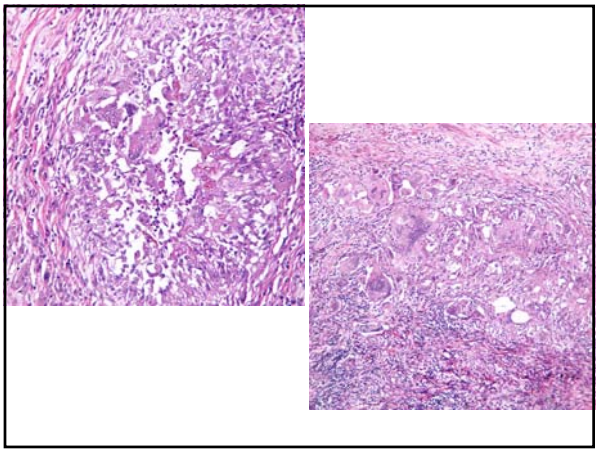
- Treatment effects
  - Reactive urothelial atypia versus dysplasia and carcinoma in-situ
  - Pseudocarcinomatous proliferation versus invasive carcinoma
  - Post-operative spindle cell nodule (PSCN) versus sarcoma

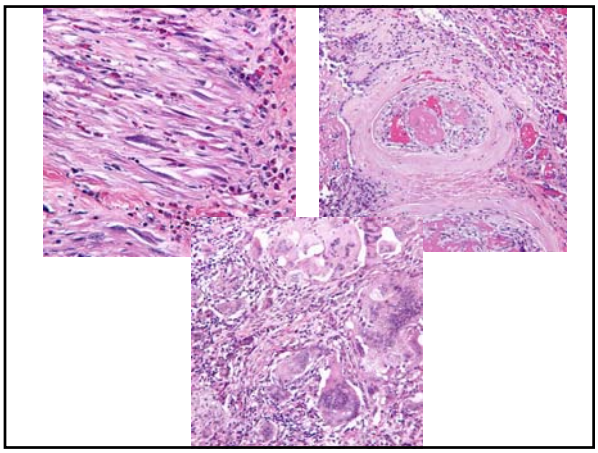
Urinary Bladder

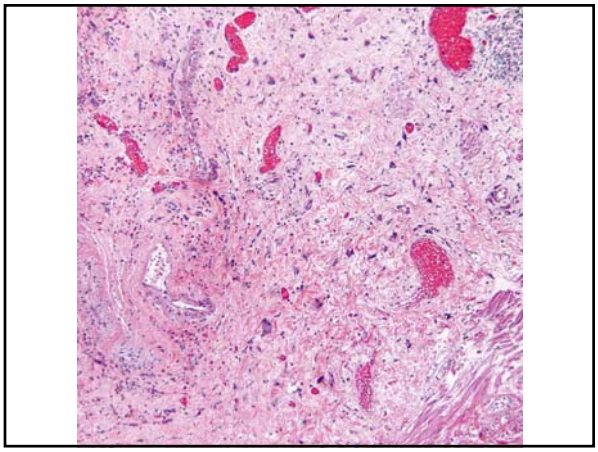
- Case 1

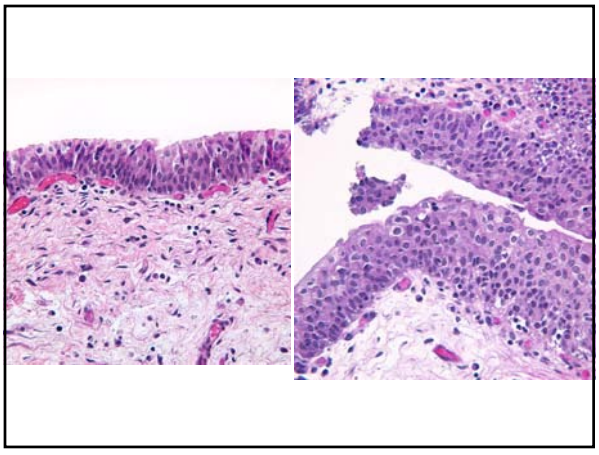
  A 65-year-old male, had prior transurethral resection of a non-invasive papillary high-grade urothelial carcinoma, followed by intravesical BCG therapy.

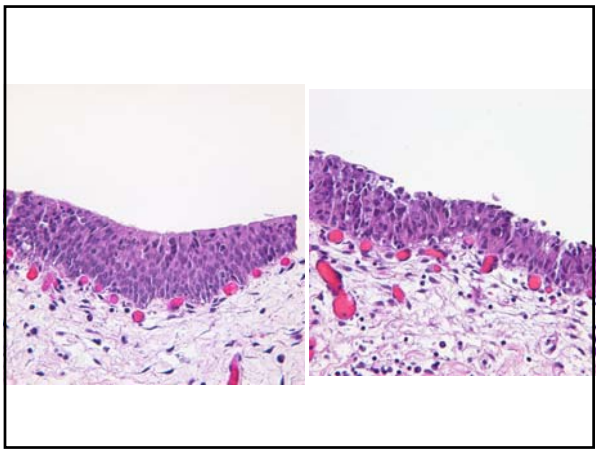
  The follow up urine cytology showed atypical urothelial cells. A cystoscopy and biopsy was performed.

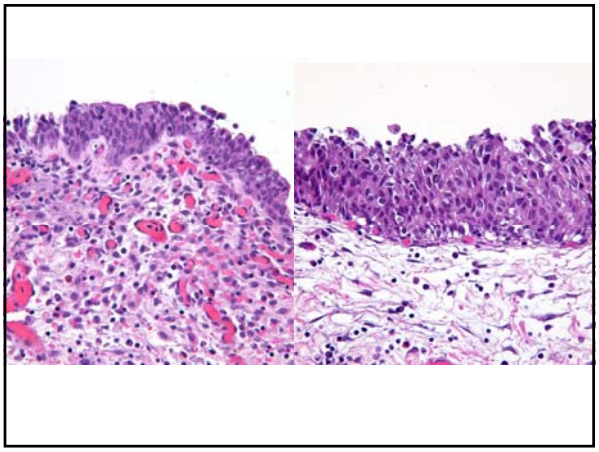


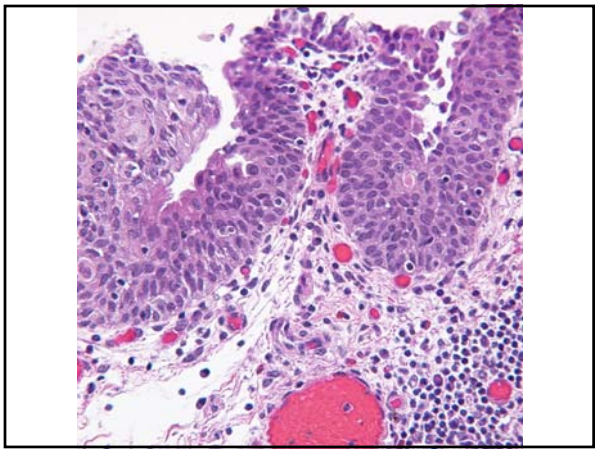


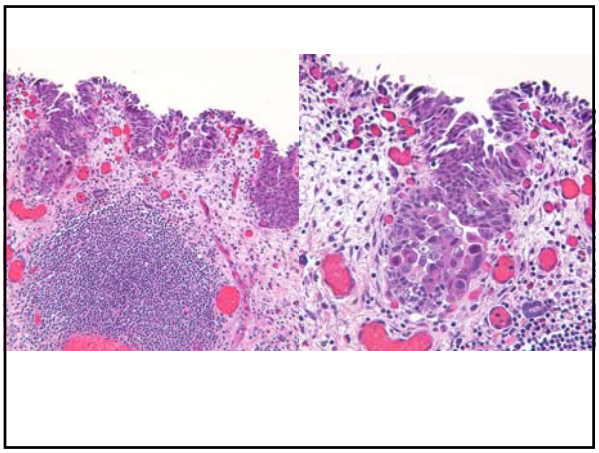


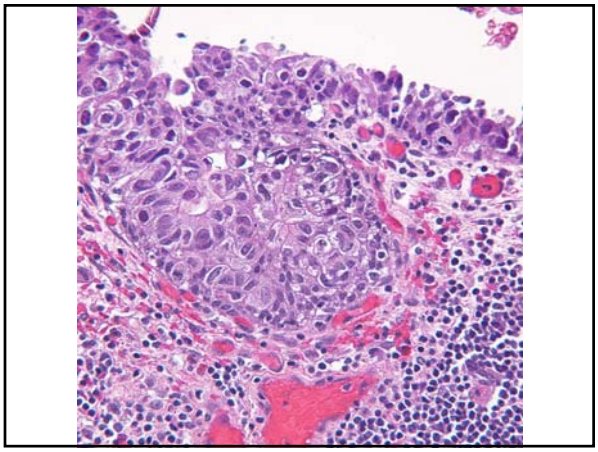


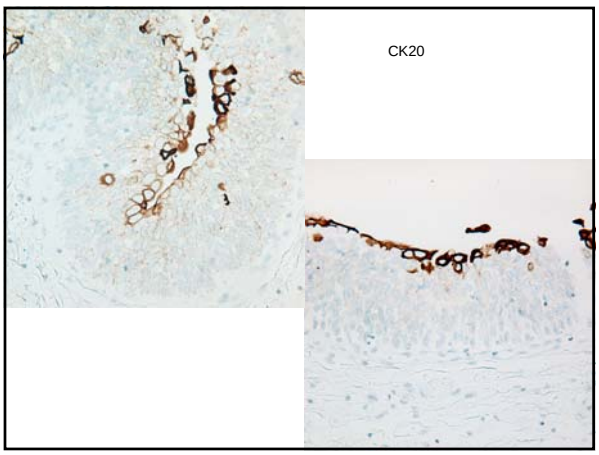


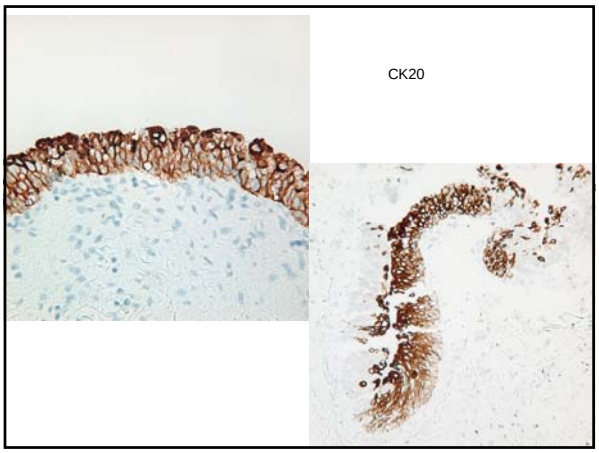









CK20



Urinary Bladder

- Case 1

  Diagnosis: Urothelial carcinoma in-situ

Learning Points

- Treatment effects
  - Reactive urothelial atypia
    - Background treatment effect
    - Low N/C ratio of the cells
    - Presence of nuclear and cytoplasmic vacuoles

Table 1 Morphologic features of flat urothelial lesions

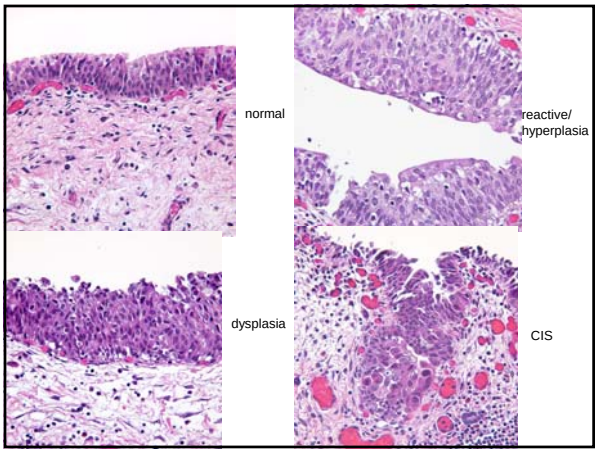
	Normal	Flat urothelial hyperplasia	Reactive atypia	AUS	Dysplasia
Architecture					
Cell layers	4-7	10 or more	Normal to mildly thickened	Normal to mildly thickened	Usually normal but may be increased or decreased
Organization of cells	Maturation from basal to superficial cell layer	Normal	Normal	Normal	Lack of maturation in basal and intermediate cell layers (not full thickness)
Cytology					
Nuclear size	Small	Normal	May be mildly enlarged	May be mildly enlarged	Variable
Nuclear shape	Round to oval	Normal	Normal	Normal	Variable
Nuclear chromatin	Smooth	Normal	Vesicular	Vesicular	Coarse
Nucleoli	Absent	Absent	Prominent	Prominent	Less prominent
Mitoses	Absent	Absent	Present in lower layers	Present in lower layers	Variable
Umbrella cells	Present	Present	Present	Present	Present

Hodges KB, Lopez-Beltran A, et al. Hum Pathol 2010;41:155-62

Table 2 Immunohistochemical features of flat urothelial lesions

	Normal	Flat urothelial hyperplasia	Reactive atypia	AUS	Dysplasia
CK20	Limited to umbrella cells	Limited to umbrella cells	Limited to umbrella cells	Increased reactivity in deeper layers	Deep layers
CD44	Limited to basal cells	Limited to basal cells	Increased reactivity in all cell layers	Increased reactivity in all cell layers	Absent
p53	Absent	Absent	Absent	Absent	Positive

Hodges KB, Lopez-Beltran A, et al. Hum Pathol 2010;41:155-62
Mckenney JK, Desai S, et al. Am J Surg Pathol 2001;25:1074-8.



Learning Points

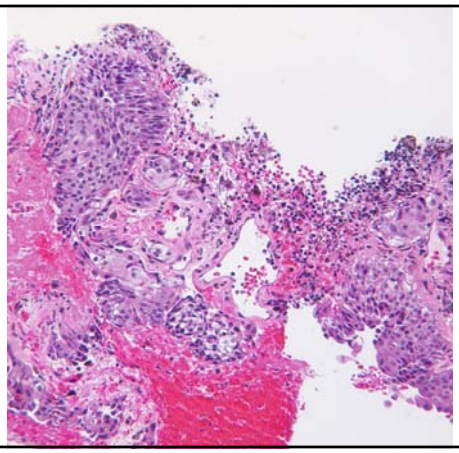
- Molecular alterations in flat urothelial lesions
  - Early carcinogenesis:
    - LOH of 9q, *FGFR3* mutation
  - Tumor progression:
    - Alterations in *DBC1*, *TP53* and *RB1*

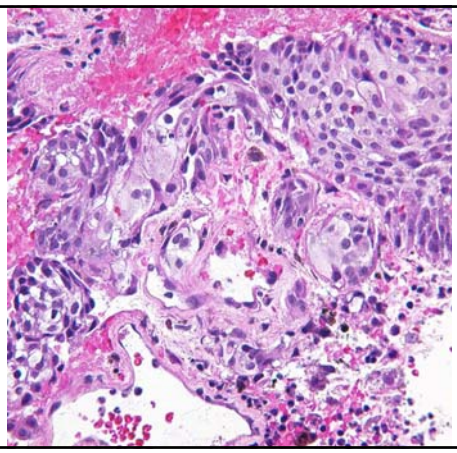
Hartmann A, Schlake G, et al. Cancer Res 2002; 62:809-18
Lee S, Jeong J, et al. Proc Natl Acad Sci 2007;104:13732-7
Lopez-Beltran A, Alvarez-Kindelan, et al. J Pathol 2008;215:263-72.

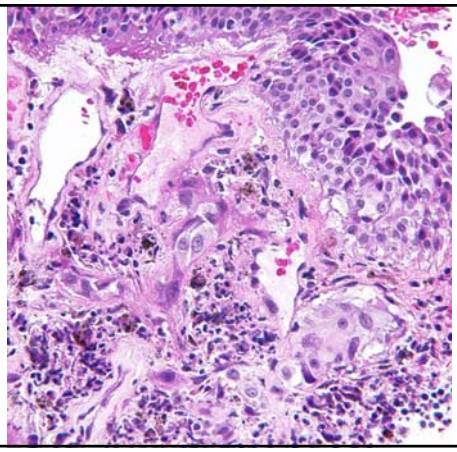
Urinary Bladder

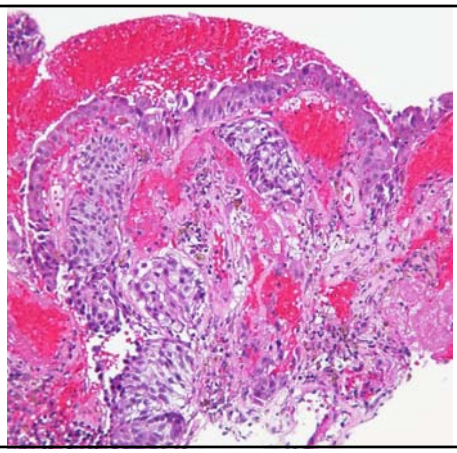
- Case 2

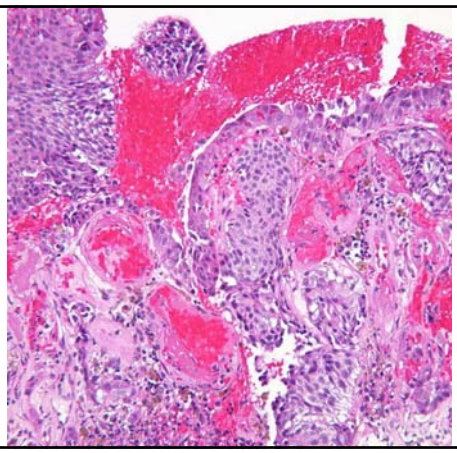
  A 69-year-old man, prior history of prostatectomy and adjuvant external beam radiation therapy for prostate cancer. Presents with gross hematuria, cystoscopy revealed two suspicious erythematous areas where were biopsied.

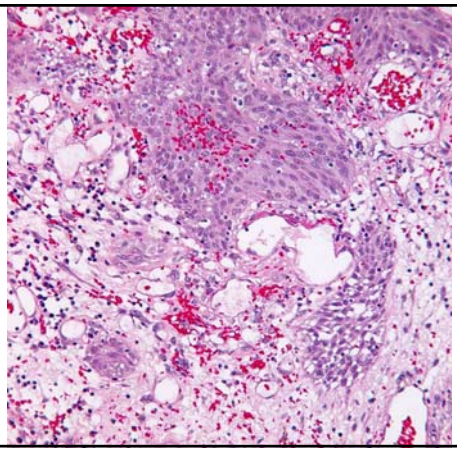


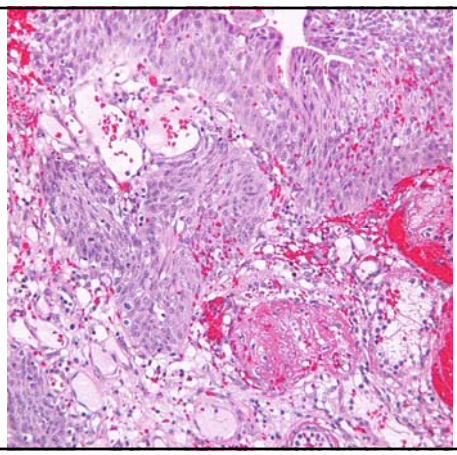


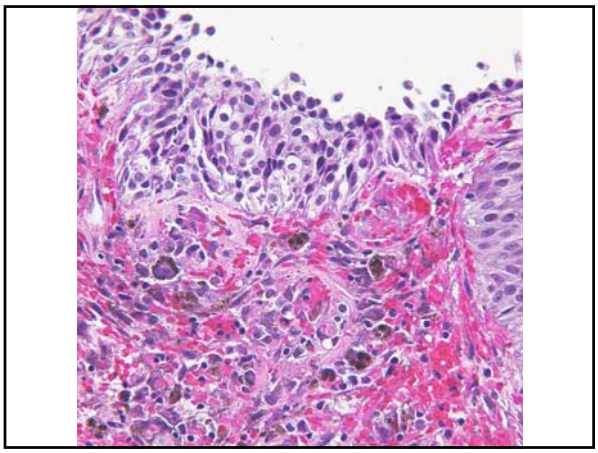


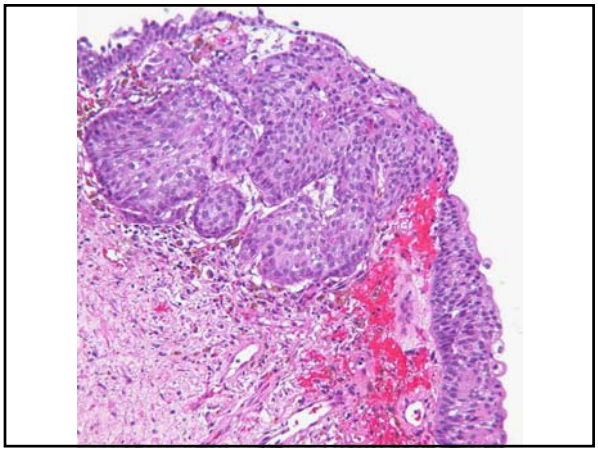


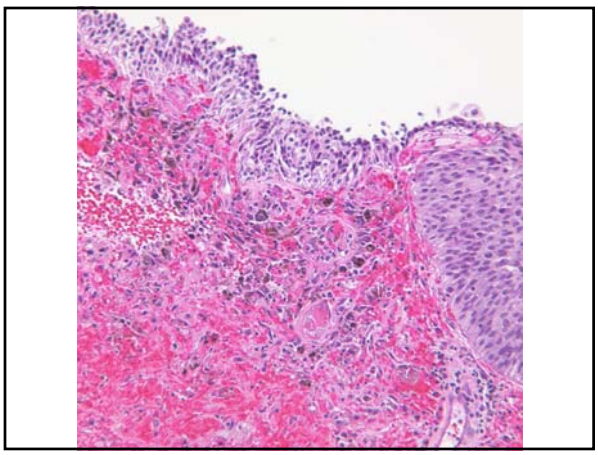












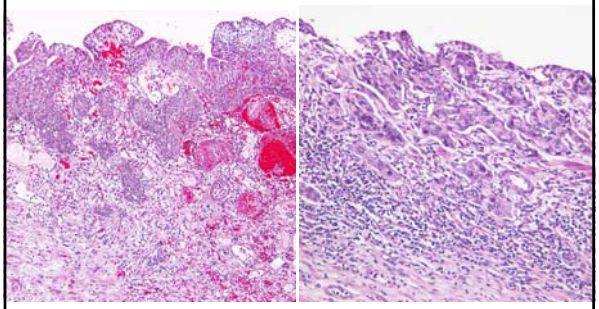
Urinary Bladder

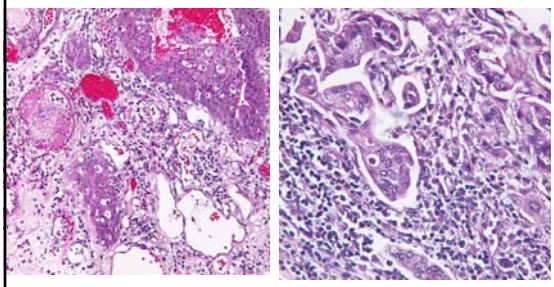
- Case 2

Diagnosis: Radiation Cystitis.

Learning Points

- Treatment effects
  - Pseudocarcinomatous proliferation
    - Mucosal ulceration with pseudoinvasive nests
    - Nests have smooth contours with paradoxical maturation
    - Cells wrapping around blood vessels
    - Vascular congestion with fibrin thrombi
    - Cells have vacuolated nuclei and cytoplasm

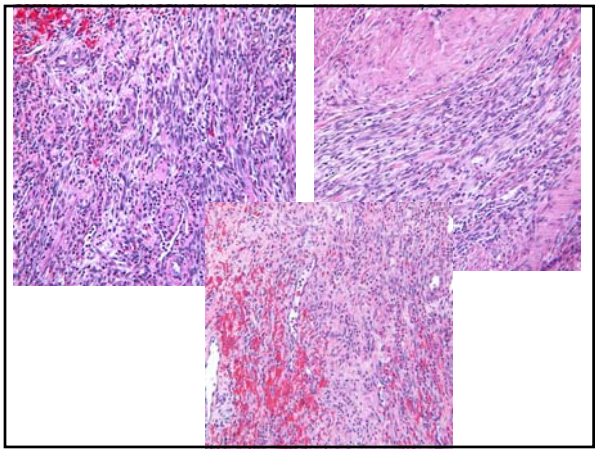


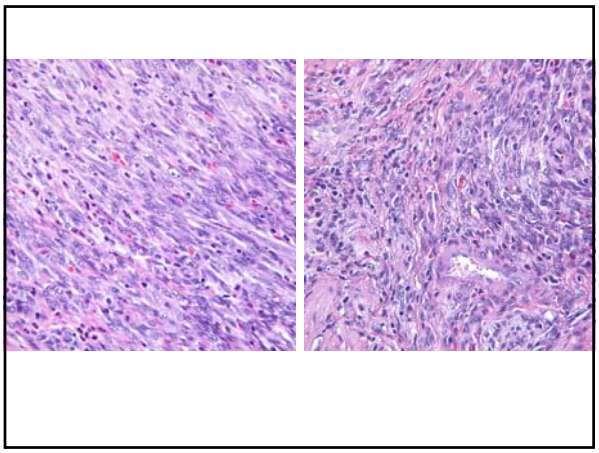


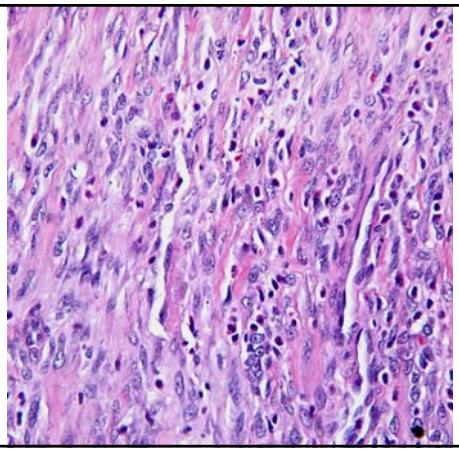
Urinary Bladder

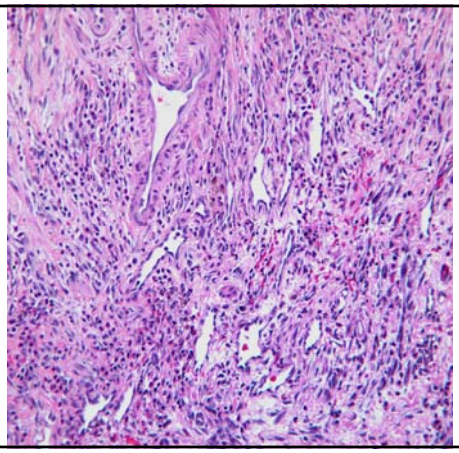
- Case 3

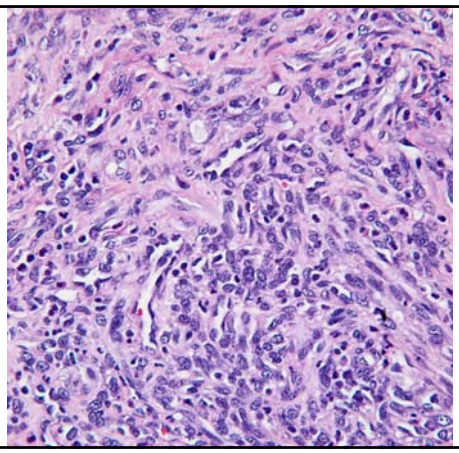
  A 55-year-old man who had a urinary bladder biopsy three months ago developed a nodular mass in the bladder wall.

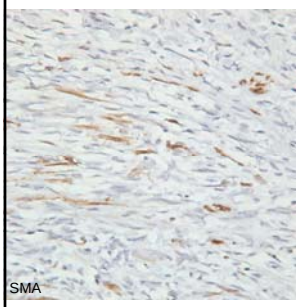


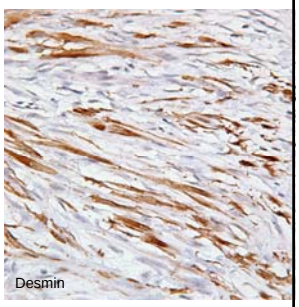












Urinary Bladder

- Case 3

Diagnosis: Postoperative spindle cell nodule

Learning Points

- Treatment effects
  - Post-operative spindle cell nodule (PSCN)
    - Recent history of resection or instrumentation (<3mon)
    - M:F 12:1
    - Most less than 1.0 cm
    - Histology
      - Cellular spindle cell proliferation associated with stromal edema
      - Delicate thin-walled vessels
      - Variable amount of inflammation
      - Mitoses (1-25/10HPFs)
    - Morphologically indistinguishable from pseudosarcomatous myofibroblastic proliferations (PMP) except for history
    - No clinical progression after complete excision

Learning Points

- Differential diagnoses

	PMP	Sarcomatoid carcinoma	Leiomyosarcoma
CK5/6	-	+	-
34betaE12	-	+	-
p63	-	+	-
SMA	+	-	+
desmin	+/-	-	+
Alk-1	+	-	-

Westfall DE, Folpe AL, et al. Am J Surg Pathol 2009;33:99-105.

Thank you!

Questions?