Adenocarcinoma of the Cervix

SAMS

Question 1. Each of the following statements about cervical adenocarcinoma is true except:

a) A majority of women with cervical adenocarcinoma have stage I tumors at diagnosis.
b) The usual clinical presentation is with abnormal vaginal bleeding.
c) Survival is relatively favorable for women with stage I tumors.
d) For inclusion in stage I, the tumor must be confined to the cervix, with no evidence of invasion of the body of the uterus or spread to the regional lymph nodes.
e) Most cervical adenocarcinomas are caused by HPV16 or HPV18.

Each of the statements is correct except:

1. a)
2. b)
3. c)
4. d)
5. e)

Statement a) is correct [A majority of women with cervical adenocarcinoma have stage I tumors at diagnosis]

- About 2/3 of patients with cervical adenocarcinoma have stage I tumors at the time of diagnosis.
- Most of the rest have stage II tumors.
- Only 8-9% of women have stage III or stage IV tumors.
Statement b) is correct [The usual clinical presentation is with abnormal vaginal bleeding]

- Most women with cervical adenocarcinoma present because of abnormal vaginal bleeding.
- Pap smears tend to be less effective at detecting adenocarcinoma than squamous cell carcinoma, but some patients are nevertheless asymptomatic and detected because they have an abnormal Pap smear.
- Patients with adenocarcinoma in situ or microinvasive adenocarcinoma are most likely to be detected because of an abnormal Pap smear.

Statement c) is correct [Survival is relatively favorable for women with stage I tumors]

- Survival is relatively favorable for women with stage I cervical cancers.
- Overall in stage I it is about 80%.
- Women with stage IA cervical cancers (less than 5 mm depth of invasion) have a very high survival rate, up to 98%
- Women with stage IB have larger tumors, and survival is related to tumor volume and presence or absence of lymph node metastases
- Survival drops off significantly in stage II, where it is only 32-37%

Statement d) is the incorrect one [For inclusion in stage I, the tumor must be confined to the cervix, with no evidence of invasion of the body of the uterus or spread to the regional lymph nodes]

- Remember, staging of cervical cancer is based on clinical parameters.
- The staging system was designed so that survival of women treated by surgery (where the uterus and lymph nodes are removed) could be compared to survival of women treated by radiotherapy, where the status of the corpus and lymph nodes is unknown.
- Stage I tumors are confined to the uterus, but they can invade the corpus and still qualify as stage I.
- The status of the lymph nodes as determined by lymph node dissections is not taken into account in the staging system.
- Therefore, women with cervical cancers can have lymph node metastases and still qualify for stage I.

Cervical Cancer Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Confined to uterus; diagnosed only by microscopy</td>
</tr>
<tr>
<td>IB</td>
<td>Confined to uterus; clinically visible or microscopically &gt; IA</td>
</tr>
<tr>
<td>II</td>
<td>Invades beyond uterus but not to pelvic wall or lower 1/3 of vagina</td>
</tr>
<tr>
<td>III</td>
<td>Extends to pelvic wall; involves lower 1/3 vagina; causes hydronephrosis</td>
</tr>
<tr>
<td>IV</td>
<td>Mucosa of bladder or rectum; beyond true pelvis; distant mets</td>
</tr>
</tbody>
</table>
Statement e) is correct [Most cervical adenocarcinomas are caused by HPV16 or HPV18]

- Most cervical adenocarcinomas are caused by HPV.
- HPV 16 and 18 are the two most common types, and are nearly equal in adenocarcinoma of the cervix.
- Quint et al found HPV 16 in 43.6% of cases, HPV18 in 41.8%, and HPV 45 in 10.9%. (Gynecol Oncol 2010;117:297-301)
- Pirog et al found HPV DNA in 91% of NOS, intestinal and endometrioid types, but not in any serous, clear cell or mesonephric types. (Am J Pathol 2000;157:1055-1062)

Question 2. When considering the differential diagnosis of adenocarcinoma in situ vs early invasive adenocarcinoma, each of the following histologic findings suggests invasion except:

- a) The tumor cells have abundant eosinophilic cytoplasm at points of possible invasion, resulting in a vaguely squamoid appearance.
- b) Numerous goblet cells are present in the abnormal glands.
- c) There is increased glandular density in the area in question.
- d) Glands are seen in close proximity to thick walled blood vessels.
- e) A stromal reaction is present around the atypical glands.

One of the 5 statements is incorrect; which is it?

1. a)
2. b) [Correct]
3. c)
4. d)
5. e)

Statement a) is correct [The tumor cells have abundant eosinophilic cytoplasm at points of possible invasion, resulting in a vaguely squamoid appearance]

- In early squamous cell carcinoma of the cervix, pathologists have observed that the tumor cells at the point of invasion often accumulate more abundant pink cytoplasm (‘pinking up of the cytoplasm’), and have vesicular nuclei with prominent nucleoli. (Journal of Clinical Pathology 56(3): 164-173)
- Similar foci of increased cytoplasmic eosinophilia occur in early invasive adenocarcinoma.
- Ostor described 7 patterns of superficial invasion. (Int J Gynecol Pathol 2000;19:29-38)
Statement b) is incorrect [Numerous goblet cells are present in the abnormal glands]

- Goblet cells occur in both adenocarcinoma in situ and invasive adenocarcinoma, so their presence does not distinguish between the two.
- ACIS with goblet cells is more common than invasive adenocarcinoma with goblet cells.
- Intestinal types of cervical adenocarcinoma can show positive staining for CK20 and CDX2, but they are also usually positive for CK7. (Int J Gynecol Pathol 2008;27:92-100)
- Staining for CK20 and CDX2 does not necessarily indicate that a cervical adenocarcinoma is secondary to an intestinal primary, but that possibility must be considered especially if staining for CK20 and CDX2 is strong and diffuse.

Statement c) is correct [There is increased glandular density in the area in question]

- Probably the most helpful feature indicating that an abnormal cervical glandular proliferation is invasive adenocarcinoma is increased glandular density – too many glands per unit area.
- Other useful findings include confluence of glands or irregularity of distribution of abnormal glands such that they cannot be viewed as being in the normal glandular field (and thus possibly as ACIS).

Statement d) is correct [Glands are seen in close proximity to thick walled blood vessels]

- The finding of glands in close proximity to thick walled (>36 microns) blood vessels suggests invasive adenocarcinoma (Int J Gynecol Pathol 2005;24:125-130).
- The glands can wrap around the blood vessels (circumferential growth), press against them (molded pattern).
- Rarely, benign glands can be near vessels, but these do not show any atypia.
- Perineural growth, if present, is also a helpful finding in identifying invasion.

Statement e) is correct A stromal reaction is present around the atypical glands]

- The presence of a desmoplastic stromal reaction around atypical glands is a helpful feature of invasive adenocarcinoma.
- Unfortunately, it is absent in many cases of early invasive adenocarcinoma.
- Minimal loosening of the stroma around atypical glands is not sufficient to diagnose invasion.
There are numerous variants of cervical adenocarcinoma. Which of the following statements about them is incorrect?

a) A villoglandular adenocarcinoma with a component of serous carcinoma is unlikely to have the highly favorable prognosis originally attributed to villoglandular adenocarcinoma of the cervix.

b) Endocervical adenocarcinomas that contain more than 10% of cells with abundant pale or clear cytoplasm and distinct cell borders are said to show ”gastric” differentiation and may have a less favorable prognosis.

c) Some minimal deviation adenocarcinoma of the mucinous type is associated with mutation of the STK11 gene, which is also mutated in the Peutz-Jeghers syndrome.

d) Minimal deviation adenocarcinoma of the mucinous type (”adenoma malignum”) almost always shows strong diffuse staining for p16, which is the most helpful immunostain for diagnosing it.

e) Mesonephric adenocarcinoma of the cervix is often associated with mesonephric hyperplasia, and is sometimes difficult to distinguish from it.

Which of the 5 statements is incorrect?

1. a)
2. b)
3. c)
4. d) ✓
5. e)

Statement a) is correct [A villoglandular adenocarcinoma with a component of serous carcinoma is unlikely to have the highly favorable prognosis originally attributed to villoglandular adenocarcinoma of the cervix]

• As originally described, villoglandular adenocarcinoma was well differentiated, with grade I nuclei and no areas of solid growth.
• It tended to occur in young women.
• It was often superficial or even non-invasive, but some women had more deeply invasive tumors.
• Nevertheless, the prognosis was highly favorable.
• The diagnosis has proven to be poorly reproducible.
• Villoglandular tumors of higher grade, and villoglandular tumors mixed with higher grade adenocarcinoma or serous or neuroendocrine carcinoma have been reported, and have a much less favorable prognosis than was initially reported for the well differentiated villoglandular adenocarcinoma (Virchows Archiv 2005;447:883-887).
• The diagnosis of well differentiated villoglandular adenocarcinoma should probably not be made on a small biopsy.

Statement b) is correct [Endocervical adenocarcinomas that contain more than 10% of cells with abundant pale or clear cytoplasm and distinct cell borders are said to show ”gastric” differentiation and may have a less favorable prognosis]

• Japanese pathologists have suggested that adenocarcinomas that contain more than 10% of cells with abundant pale or clear cytoplasm and distinct cell borders show ”gastric” differentiation (Am J Surg Pathol 2007;31:664-672).
• The distinctive tumor cells resemble pyloric cells.
• Staining for HIK 1083, a gastric mucin antibody, helps confirm the diagnosis.
• The tumors also often stain for MUC6, but this is less specific.
• Most mucinous minimal deviation adenocarcinomas fall into the ”gastric” category.
• Patients with “gastric” type adenocarcinoma have had a less favorable prognosis in Japanese reports, but there are no reports of this type of adenocarcinoma from Western pathologists for comparison.
Statement c) is correct [Some minimal deviation adenocarcinoma of the mucinous type is associated with mutation of the STK11 gene, which is also mutated in the Peutz-Jeghers syndrome]

- It has been known for some time that women with the Peutz-Jeghers syndrome are at increased risk of developing mucinous minimal deviation adenocarcinoma of the cervix. 3/26 patients reported by Gilks et al had the PJ syndrome (Am J Surg Pathol 1989;13:717-729).
- The Peutz-Jeghers syndrome has been shown to be associated with a mutation of the STK11 gene located at 19p13.3
- Mutation of the STK11 gene also occurs in patients who do not have the Peutz-Jeghers syndrome (6/11 in one recent series).
- Patients with the mutation had a worse prognosis (Lab Invest 2003;83:35-45.

Statement d) is the incorrect one [Minimal deviation adenocarcinoma of the mucinous type (“adenoma malignum”) almost always shows strong diffuse staining for p16, which is the most helpful immunostain for diagnosing it]

- In general, I have not found immunostains to be particularly helpful in diagnosing MDA.
- MDA often shows positive staining for HIK1083, not available here, and thus has a “gastric” phenotype.
- HPV DNA is typically not demonstrated in this type of carcinoma.
- Absence of an association with HPV results in negative staining for p16 in most instances.
- Lack of staining for PAX2 may suggest a diagnosis of carcinoma vs endocervical glandular hyperplasia.

Statement e) is correct [Mesonephric adenocarcinoma of the cervix is often associated with mesonephric hyperplasia, and is sometimes difficult to distinguish from it]

- Mesonephric remnants have been described around mesonephric adenocarcinoma in most cases.
- Clement found them in 7 of 8 cases, Silver in 10/11 cases, but Bague only in 5/9. I have seen them in 2/3 cases.
- The remnants often show increased atypia near the carcinoma.
- Diffuse hyperplasia is particularly difficult to differentiate from mesonephric hyperplasia, and since sampling can be an issue, I do not think that this type of hyperplasia should be diagnosed unless proven by findings in a hysterectomy specimen.

Yolk Sac Tumor of the Ovary and Extraovarian Sites in Women

SAMS Questions
Question 1. Following are some statements about yolk sac tumor of the ovary. One is false; which is it?

a) Yolk sac tumor of the ovary has a similar age distribution as serous carcinoma.
b) Most patients have an elevated serum alpha-fetoprotein level.
c) The CA-125 levels are commonly elevated.
d) About 50% of patients have clinically obvious extraovarian spread at diagnosis.
e) Effective chemotherapy is now available, and most patients can be cured.

Following are some statements about yolk sac tumor of the ovary. One is false; which is it?

1. a) 
2. b) 
3. c) 
4. d) 
5. e) 

Statement a) is the false one. [Yolk sac tumor of the ovary has a similar age distribution as serous carcinoma]

- Serous carcinoma is uncommon in women less than 40 years of age, and the risk increases with age after that.
- Most cases of yolk sac tumor occur in young women and children.
- The average age is 19 years.
- In a literature review in 2001, yolk sac tumor had been reported in only 5 patients >50 years old.
- Think twice about diagnosing yolk sac tumor in a patient older than 50.

Statement b) is true. [Most patients have an elevated serum alpha-fetoprotein level]

- The serum alpha-fetoprotein is almost always elevated if it is tested for.
- Germ cell tumors are uncommon, and few clinicians see cases, so the AFP level is frequently not measured.
- AFP has a half life of 3-6 days, so a postoperative test may be informative.
- An elevated AFP suggests that a tumor may contain yolk sac tumor; the pathologist should search carefully for it.
- AFP is an excellent clinical marker for use in therapy of patients with yolk sac tumor.
- If the AFP does not drop to baseline after treatment, residual tumor is present.
- If the AFP becomes elevated after treatment the tumor has recurred and further therapy is required.

Statement c) is true. [The CA-125 levels are commonly elevated]

- While CA125 is often viewed as a marker for serous carcinoma and related tumors, it is not specific.
- Lower levels, but still significant elevations are seen in patients with yolk sac tumors.
- In one study, 5/5 patients had moderately increased levels of CA125. (Int J Gynaecol Obstet 1997;58:323-324)
- Other conditions associated with an elevated CA125 include pregnancy, endometriosis, PID, leiomyomas, liver disease, and some collagen-vascular diseases.

Statement d) is true. [About 50% of patients have clinically obvious extraovarian spread at diagnosis]

- About 50% of patients with yolk sac tumors have stage I tumors.
- Survival in patients with untreated stage I tumors is poor.
- In the Kurman and Norris series, pre-chemotherapy for the most part, only 8 of 49 stage I patients survived.
- Subclinical metastases are present in a majority of patients with stage I tumors.
- Patients with stage I tumors require adjuvant chemotherapy.
- Accurate diagnosis is required for optimum therapy.

Statement e) is true. [Effective chemotherapy is now available, and most patients can be cured]

- Fortunately, effective chemotherapy is now available for germ cell tumors of all types.
- 12/13 stage I patients and 16/22 overall treated with VAC (vincristine, actinomycin-D, and cyclophosphamide) at MD Anderson in the 1980’s survived.
- Three cycles of BEP (bleomycin, etoposide, cisplatin) is the current standard. (Cancer Treat Rev 2008;34:427-441)
- Best results are obtained in patients with localized (stage I) disease, where survival is close to 100%.
- Patients with advanced or recurrent disease are also generally treatable.
Question 2. Each of the following findings supports a diagnosis of yolk sac tumor except for:

a) The tumor is unilateral.
b) A microcystic pattern of growth is readily identified.
c) Schiller-Duval bodies are identified in the tumor.
d) The tumor cells show strong nuclear staining for OCT4
e) The tumor cells show cytoplasmic staining for Glypican 3.

a) Supports yolk sac tumor. [The tumor is unilateral]

- Yolk sac tumor is almost invariably unilateral.
- Bilaterality suggests metastatic spread.
- This is characteristic of all malignant germ cell tumors.
- Only dysgerminoma has any likelihood of being bilateral, in up to 15% of cases. (7 of 105 at AFIP)
- If a tumor is present in the contralateral ovary it may be a benign cystic teratoma.

b) Supports yolk sac tumor. [A microcystic pattern of growth is readily identified]

- The reticular or microcystic pattern is one of the most characteristic of yolk sac tumor.
- Other common patterns include solid, endodermal sinus, papillary, myxoid, and PVV
c) Supports yolk sac tumor. [Schiller-Duval bodies are identified in the tumor]

- Schiller-Duval bodies are vaguely glomeruloid structures with a fibrovascular core and a lining of cuboidal to columnar tumor cells.
- They are said to be diagnostic of yolk sac tumor.

![Schiller-Duval bodies](image)

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d) Does not support yolk sac tumor. [The tumor cells show strong nuclear staining for OCT4]

- OCT4 is a stem cell/primitive germ cell marker.
- In ovarian tumors, positive staining is seen in dysgerminoma, gonadoblastoma, and embryonal carcinoma.
- Positive staining for OCT4 would rule out yolk sac tumor.
- A marker that is often positive in yolk sac tumor as well as dysgerminoma/embryonal carcinoma is SALL4.

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e) Supports yolk sac tumor. [The tumor cells show cytoplasmic staining for Glypican 3]

- The primitive germ cell markers stain nuclear transcription factors. A positive result is nuclear staining.
- A variety of cytoplasmic stains can be used to test tumors thought to be yolk sac tumors.
- Two good cytoplasmic markers for yolk sac tumor are alpha-fetoprotein, the traditional marker, and glypican-3, a newer marker.
- Glypican -3 is positive in up to 100% of yolk sac tumors.
Question 3. Which of the following statements about extraovarian yolk sac tumors is not correct?

1. a) The most common extragonadal site for yolk sac tumor in the pelvis is in the vagina.
2. b) Yolk sac tumors involving the peritoneum, like our case, are rare.
3. c) Extraovarian yolk sac tumors occur in elderly patients, rather than in the younger population characteristic of ovarian yolk sac tumor.
4. d) Extraovarian yolk sac tumors show the same histologic and immunohistochemical features as ovarian yolk sac tumors.
5. e) The differential diagnosis can include metastatic hepatocellular carcinoma.

**Yolk Sac Tumor Immunohistochemistry**

<table>
<thead>
<tr>
<th>Stain</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin AE1/AE3</td>
<td>+ Cytoplasm</td>
</tr>
<tr>
<td>EMA, CK7</td>
<td>-</td>
</tr>
<tr>
<td>OCT4, NANOG</td>
<td>-</td>
</tr>
<tr>
<td>SALL4</td>
<td>+</td>
</tr>
<tr>
<td>Glypican 3</td>
<td>+</td>
</tr>
<tr>
<td>Alpha-fetoprotein</td>
<td>+</td>
</tr>
<tr>
<td>CD30</td>
<td>-</td>
</tr>
<tr>
<td>CD117 (c-kit)</td>
<td>-</td>
</tr>
<tr>
<td>D2-40, PLAP</td>
<td>- or minimal</td>
</tr>
</tbody>
</table>

Question 3. Which of the following statements about extraovarian yolk sac tumors is not correct?

1. a)
2. b)
3. ✗ c)
4. d)
5. e)
Statement a) is correct. [The most common extragonadal site for yolk sac tumor in the pelvis is in the vagina]

- Before their true nature was recognized these were called “carcinoma of the infant vagina.”
- Traditional therapy has included radical surgery followed by chemotherapy, but more conservative treatment with biopsy followed by chemotherapy has been considered. (J Pediatr Hematol Oncol 2006 28:768-771)
- Histologic features are similar to those in yolk sac tumors at other sites.

Statement b) is correct. [Yolk sac tumors involving the peritoneum, like our case, are rare]

- Extraovarian yolk sac tumor at any site is uncommon.
- Only 10 cases of extraovarian yolk sac tumor have been reported in the peritoneum.
- Tumor size ranges up to about 10 cm.
- Serum AFP has been elevated when measured.

Statement c) is incorrect. [Extraovarian yolk sac tumors occur in elderly patients, rather than in the younger population characteristic of ovarian yolk sac tumor]

- Patient demographics for ovarian and extraovarian yolk sac tumors are similar with some exceptions.
- Yolk sac tumor of the vagina is a tumor of children, usually occurring in patients from 6 months to 2 years of age (Gynecol Oncol 1984;18:380-392)
- Patients with abdominal yolk sac tumors have ranged from 1.8 years to 33 years.
- No patients like ours, a 59 year old postmenopausal woman, have been reported.
- The possibility of an origin from a somatic carcinoma arising in endometriosis should be considered if the patient is elderly.

Statement d) is correct. [Extraovarian yolk sac tumors show the same histologic and immunohistochemical features as ovarian yolk sac tumors]

- The histologic features are similar to those of ovarian yolk sac tumors.
- Any of the variants can be detected.
- The immunohistochemical features are similar to those of ovarian yolk sac tumors, so immunostains can help confirm the diagnosis.
Statement e) is correct. [The differential diagnosis can include metastatic hepatocellular carcinoma]

- The yolk sac and the liver are both endodermal structures, with some functions, such as hematopoiesis, in common.
- There are similarities in the histology and immunohistology between yolk sac tumors and liver tumors.
- Secretion of alpha-fetoprotein and staining for glypican-3 are examples.
- There is a hepatoid variant of yolk sac tumor in which the tumor cells resemble liver cells.
- These can be particularly difficult to differentiate from metastatic hepatocellular carcinoma.
- Use of some of the newer immunostains, such as SALL4, can be particularly helpful in the differential diagnosis.