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REVIEW

Ovarian Cancer: Many Diseases Under One Name

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In the United States, ovarian cancer is the second most common form of gynecologic cancer and the second leading cause of gynecologic cancer death. It is a heterogeneous disease with many different types and subtypes. The most common variety (70%-80%) is the high-grade serous epithelial tumor. A positive family history and/or the presence of susceptibility genes (BRCA1, BRCA2, and mismatch repair genes) increase the risk for developing the disease. Due to the lack of effective screening tools, even in those with known increased risk, most ovarian cancers are diagnosed at advanced stages. Diagnosis and accurate staging usually require tissue sampling and extensive debulking surgery performed by a surgeon who specializes in gynecologic oncology. Combination chemotherapy, before or after surgery, or as primary treatment for advanced disease is commonly needed. Mortality rates vary by stage, grade, and type of tumor. For the most common histotypes, due to the presence of advanced disease at presentation in most individuals, overall death rates remain high. Survival is better with some of the less common subtypes including sex cord stromal, germ cell and borderline epithelial ovarian tumors.

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Key words: Epithelial ovarian tumors, sex cord - stromal tumors, germ cell tumors, high-grade serous carcinoma, low-grade serous carcinoma, endometroid carcinoma, primary mucinous carcinoma, carcinosarcoma, borderline ovarian carcinoma, BRCA1 and BRCA2, hereditary nonpolyposis coli/HNOCC/Lynch syndrome, fallopian tube cancer, primary cancer of the peritoneum, cancer antigen-125 (CA-125), human epididymis secretory protein-4 (HE-4).

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Worldwide ovarian malignancies are the third most common cancer of the female reproductive organs (324,603, 18th overall) and the second leading cause of death from gynecological malignancies, behind cervical tumors (206,956, 14th overall). In the United States, it is the second leading cause of gynecological cancers (18th overall) and the second leading cause of death behind uterine tumors. In the United States, it is estimated that there will be 20,890 new cases of ovarian cancer and 12,730 deaths in 2025, representing 1.0% and 2.1% of all new cancer cases and deaths, respectively. Approximately, 1.1% of US women will be diagnosed with ovarian cancer in their lifetime.[1-4]

Ovarian cancer is a heterogenous disease with multiple different types and subtypes. Overall, it is divided into 3 major categories. These categories include epithelial, germ cell, and sex cord-stromal tumors. The most common, representing about 90% of the malignancies, are the epithelial cancers that arise from the cells lining the surface of the ovary. The germ cell tumors arise from the egg components or germ cells in the glands. Sex cord-stromal tumors develop from the support structures. The frequency of the latter 2 types is much less and falls in the 2% to 7% range for each in various studies.[5]

Epithelial carcinomas of the ovary also include similar tumors of the fallopian tube and peritoneum. They are all considered variants of the same condition. In fact, the serous lesions, both high- and low-grade, are felt to likely originate in the fallopian tubes.

There are multiple histologic subtypes (histotypes) of the epithelial variety. The most common (70% to 80%) is high-grade serous carcinoma (HGSC). Other, less common histotypes, include endometroid (10%), clear cell (5% to 10%), mucinous (3%), low-grade serous (LGSC), which occurs in <5% of cases, and carcinosarcoma (3%). The latter represents a mixture of carcinoma and sarcoma malignant cells. In addition, there are borderline malignant versions of the serous, endometroid, mucinous, and clear cell histotypes.[6,7]

HGSC is the most common type of ovarian carcinoma and generally occurs at a mean age in the mid to late 50s, usually at an advanced stage. Disease confined to the ovary is uncommon (10% of cases or less). It may be associated with the BRCA1 and BRCA2 mutations. LGSC occurs much less frequently and, despite having a serous histology, appears to be a distinct clinical entity when compared to the high-grade lesions with different genetic mutations and a slower growth pattern. However, like HGSC, it is frequently diagnosed at advanced stages. The 2 different serous subtypes also differ in their response to chemotherapy.[6,8]

Endometroid carcinoma is thought to originate from endometriosis, responds better to chemotherapy, is associated with Lynch syndrome and uterine cancer, and more typically presents at an early stage. However, when found at a higher stage, it clinically behaves like HGSC.

The clear cell histotype is like endometroid in that it is thought to originate from endometriosis, is associated with Lynch syndrome and often presents in early stages. However, in advanced stages, it often does poorly as it is resistant to chemotherapy.[6,8]

Primary mucinous carcinoma of the ovary may be difficult to differentiate from metastasis from the gastrointestinal tract based on histology alone, and immunohistochemistry staining is often required as well. These tumors usually present in an early stage of disease. Carcinosarcomas are highly aggressive, tend to present in an older population, and are resistant to chemotherapy, leading to a generally poor prognosis.[6,8,9]

The borderline lesions (formerly known as tumors of low malignant potential) are characterized by increased cellular proliferation with atypia but without local invasion of the ovarian stroma and represent up to 15% of all ovarian cancers. Most of these lesions are confined to the ovary but some spread intraperitoneally. The serous variety is the most common, followed by the mucinous type (approximately 95% together). The others occur much less frequently.[6,10-12]

Sex-cord-stromal tumors develop from the sex cord and/or stromal or supportive structures of the ovary. These include Sertoli cells, granulosa cells, theca cells, Leydig or Sertoli-Leydig cells combined, fibromas, steroid cells, and gynandroblastomas that combine Sertoli-Leydig and granulosa cells. The mean age of onset is approximately 50, may have a familial basis, and are associated with some genetic mutations but not BRCA.[13,14]

Germ cell tumors develop from germ cell structures in the ovary and progress toward embryo like or placenta like lesions. These malignancies include immature or malignant mature teratoma, dysgerminoma, embryonal carcinoma, mixed germ cell tumors, polyembryoma, yolk sac or endodermal sinus tumors and occasionally malignant transformation of gonadoblastoma. They tend to occur in younger women (ages 10 to 30).[15]

The risk factors for epithelial ovarian cancer include being postmenopausal, older age, infertility/nulliparity, endometriosis, polycystic ovarian syndrome, smoking (for mucinous carcinoma), a positive family history (relative risk varies from 1.19 to 1.75 for different histotypes for disease in first degree relatives) and the presence of susceptibility genes including BRCA1 and BRCA2 and the hereditary nonpolyposis coli/HNOCC/Lynch syndrome (due to mutated mismatch repair genes). Things that reduce the risk for developing ovarian cancer include bilateral salpingo-oophorectomy

(most effective), prolonged use of oral contraceptives, tubal ligation, breastfeeding and multiparity.[8,16-18]

Ovarian cancer is notoriously difficult to diagnose in early stages. The associated symptoms are common in the population and often overlap with those from benign conditions. These symptoms include bloating, urinary frequency or urgency, early satiety or feeling full, and abdominal or pelvic pain. The presence of other history or findings such as abdominal distention, a positive family history of ovarian cancer or BRCA or Lynch mutations and postmenopausal bleeding, increases the suspicion for the diagnosis but are still non-specific. Consequently, most women are diagnosed with advanced disease.[19]

Several different tumor biomarkers have been associated with one or more of the various types or subtypes of ovarian cancer. These include cancer antigen-125 (CA-125), human epididymis secretory protein 4 (HE4), inhibin A and B, carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9), alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH). Some of these are more specific for certain variants, such as mucinous epithelial carcinoma (inhibin, CA 19-9), malignant germ cell tumors (AFP, HCG, LDH), and granulosa cell tumors (inhibin). Others are more non-specific indicators of the presence or extent of malignancy (CEA, LDH). In addition, there are several multivariate index assays that combine multiple factors, including the Risk Malignancy Index (RMI) Assay, OVA1 Assay, Risk of Ovarian Malignancy Algorithm (ROMA) Assay. All these tools may be used alone or in combination to aid in diagnosis, prognostic assessment, and for following treated individuals (to assess for evidence of inadequate response or recurrence). The CA-125 is the tumor marker most commonly utilized in current clinical practice.[12,14,20,21]

Several newer approaches that show promise but that are not currently widely available are the detection of microRNA's (short RNA molecules that are abnormal in cancer and act like tumor specific defective suppressor or oncogenes), cell free DNA (cf DNA) methylation patterns (indicative of malignant transformation), and circulating tumor cells. These novel tools potentially hold the promise of detection of disease at an early stage of presentation and identification of recurrent disease while still treatable. However, biologic and technical factors still limit their usefulness in practice.[19,20,22]

With the current tools, screening for ovarian cancer has not proved effective in reducing mortality because it is a low-prevalence disease, and the currently available tools are limited in effectiveness by their sensitivity and specificity (reducing positive and negative predictive value). Attempts at screening have been made using different tools, including a combination of cancer antigen 125 (CA-125) and transvaginal ultrasound but have not demonstrated a reduction in death rates, even in individuals who are at higher risk due to family history or known genetic mutations. The most effective approach for reducing deaths in the latter scenarios is prophylactic surgery with bilateral salpingo-oophorectomy.[23]

The diagnosis of ovarian cancer can be suspected based on clinical findings such as the above-noted clinical symptoms or the development of signs of the disease, such as new onset ascites or pleural effusion, bowel obstruction, vaginal bleeding, or venous thromboembolism. Findings on physical examination (adnexal mass, atypical glandular cells on cervical cytology) or other testing (increased CA-125, CEA, HE4 level or others) or imaging done for cause or other reasons (abdominal and/or pelvic ultrasound, positron emission tomography (PET), CT or MRI scans) can strongly suggest the presence of the disease. However, definitive diagnosis of ovarian cancer depends on histologic examination of tissue from the ovary, fallopian tube or peritoneum or analysis of fluid collected from the thoracic or abdominal cavity.[15,24]

Table 1. Ovarian Carcinoma TNM Staging AJCC UICC 8th Edition

Primary Tumor (T)		
T Category	FIGO Stage	T Criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to ovaries (one or both) or fallopian tube(s)
T1a	IA	Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1b	IB	Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1c	IC	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
T1c1	IC1	▪ Surgical spill
T1c2	IC2	▪ Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c3	IC3	▪ Malignant cells in ascites or peritoneal washings
T2	II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
T2a	IIA	Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries
T2b	IIB	Extension to and/or implants on other pelvic tissues
T3	III	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes
T3a	IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3b	IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension with or without metastasis to the retroperitoneal lymph nodes
T3c	IIIC	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
Regional Lymph Nodes (N)		
N Category	FIGO Stage	N Criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	IIIA1	Positive retroperitoneal lymph nodes only (histologically confirmed)
N1a	IIIA1i	Metastasis up to and including 10 mm in greatest dimension
N1b	IIIA1ii	Metastasis more than 10 mm in greatest dimension
Distant Metastasis (M)		
M Category	FIGO Stage	M Criteria
M0		No distant metastasis
M1	IV	Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine
M1a	IVA	Pleural effusion with positive cytology
M1b	IVB	Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine

Table 1. Continued

Prognostic Stage Groups			
T	N	M	Stage
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T1c	N0	M0	IC
T2	N0	M0	II
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T1/T2	N1	M0	IIIA1
T3a	NX, N0, N1	M0	IIIA2
T3b	NX, N0, N1	M0	IIIB
T3c	NX, N0, N1	M0	IIIC
Any T	Any N	M1	IV
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB

The staging of ovarian cancer requires an extensive surgical evaluation by a specially trained gynecologic surgeon. This includes a total hysterectomy with bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, omentectomy, and evaluation of the peritoneal surfaces with biopsies of suspicious areas. Furthermore, cytologic analysis of pelvic washings is performed when overt cancer spread is not evident. When metastases are evident, surgical debulking or removal of as much gross evidence of the malignancy as possible is performed.[15,25]

There are two systems for staging ovarian cancer. These are the American Joint Committee on Cancer (AJCC) system, which uses the extent of the tumor (T), lymph node involvement (N) and presence of metastasis (M) approach and the International Federation of Gynecology and Obstetrics (FIGO) systems. The two systems are very similar in their results and can be summarized in Table 1.[26]

The treatment of epithelial ovarian cancer varies primarily by the stage but also the grade and histotype of the tumor. Low-grade stage IA and IB cancers are usually treated with surgical resection of the lesion. For high-grade stages I cancers the addition of chemotherapy is recommended (adjuvant therapy). For higher stage lesions (II, III) with a possibility of cure, recommended therapy is debulking surgery to remove all visible and palpable evidence of cancer, followed by chemotherapy. In cases where it is unlikely that all the gross evidence of malignancy can be removed surgically, chemotherapy may be administered first (neoadjuvant therapy) to shrink the lesions and make them more amenable to surgical removal. Although stage IV disease is not curable, the best cases may be treated as stage III above with the goal of optimizing palliation.[8,20,27]

The best option for chemotherapy is a combination of a platinum-based drug and a taxane, most commonly carboplatin (Paraplatin) and paclitaxel (Taxol) given over 6 cycles. High-grade serous and endometroid cancers are generally highly sensitive to this regimen, while the low-grade serous, clear cell and mucinous lesions are relatively resistant. One alternative agent is bevacizumab (Avastin), a monoclonal antibody that is active against vascular endothelial growth factor (VEGF) that works by interrupting the blood flow to the cancer. Other treatments are in a class of drugs called poly (ADP-ribose) polymerase or PARP inhibitors. These agents are especially effective

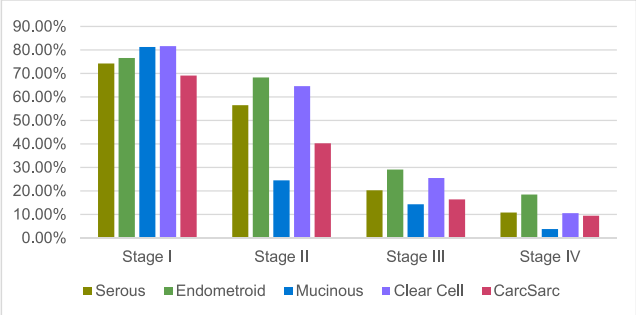

Figure 1. *High grade ovarian cancer survival by histotype and stage - 14 years.*

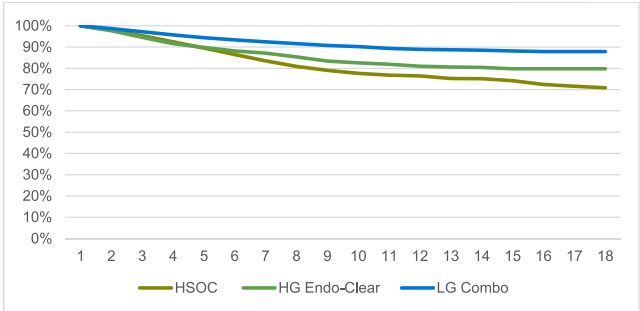

Figure 3. *Cumulative Dis Spec survival by histotype combinations stage I.*

in individuals with BRCA1/BRCA2 mutations. They include olaparib (Lynparza), niraparib ((Zejula) and rucaparib (Rubraca). Hyperthermic intraperitoneal chemotherapy is also used. However, despite these different treatment options, recurrence is common.[8,20,28-30]

For individuals with ovarian sex cord-stromal or germ cell tumors the surgical staging and treatment are like that used for epithelial ovarian cancer. In addition, the use of adjuvant or primary chemotherapy is similar as well. The chemotherapy used for each is platinum based but generally somewhat different than that for epithelial cancer.[31,32]

Multiple papers indicate that survival with epithelial ovarian cancer varies with the histotype, stage and grade of the cancer. Ovarian cancer mortality can broadly be separated by whether the cancer is high grade or low grade. Survival is better with the low-grade tumors, although with both groupings the survival steadily deteriorates with an increasing stage. On a stage for stage basis, mortality is greater with the high-grade histology (see Figures 1 & 2). Clinical papers confirm that most of the deaths that occur with the disease are due to the cancer itself and are not the result of other causes. As noted previously, the overall mortality associated with ovarian cancer is high because most cases are diagnosed in advanced stages (III or IV).[33-37]

An analysis using the Surveillance Epidemiology End Results (SEER) national cancer database provides insights into the pattern of mortality associated with the disease.

1. Within each grade and stage grouping there is variation of the survival based on the histotype.
2. High-grade serous ovarian cancer has relatively poor survival for all stages.
3. Except for stage I, mucinous cancer has reduced disease specific survival compared other subtypes for both high- and low-grade cancers.
4. Endometroid lesions generally have a modestly better survival in all grade and stage lesions.

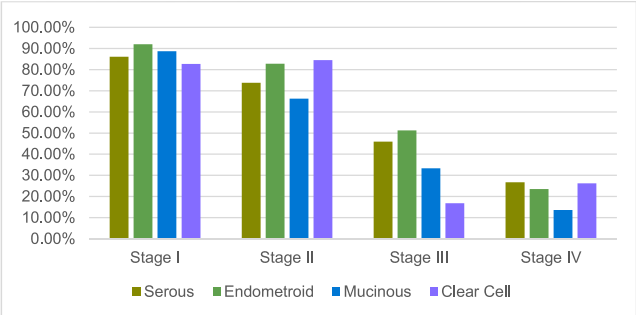

Figure 2. *Low grade ovarian cancer survival by histotype and stage - 14 years.*

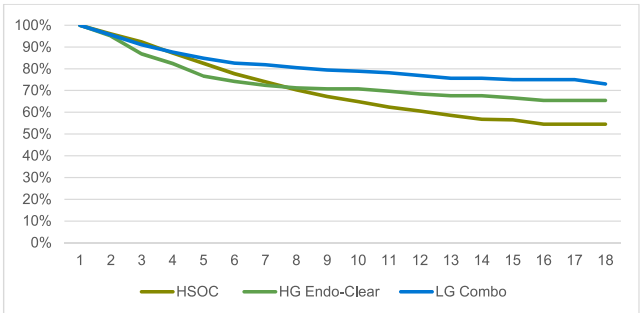

Figure 4. *Cumulative Dis Spec survival by histotype combinations stage II.*

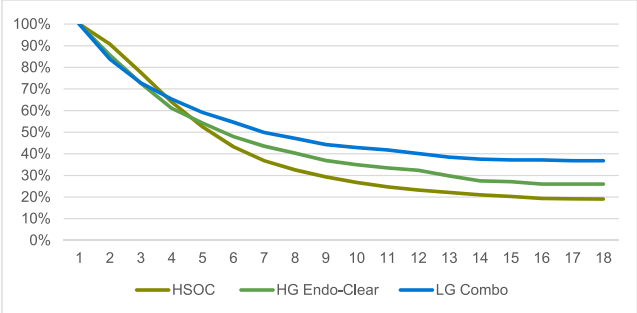

Figure 5. *Cumulative Dis Spec survival by histotype combinations stage III.*

5. Survival with carcinosarcoma (all grades combined) is lower than high grade serous carcinoma in stages I and II but is comparable to that histotype in stages III and IV.
6. When dividing the total population into 3 groups – high-grade serous, the combination of high-grade endometroid and clear cell and low-grade serous, endometroid, mucinous and clear cell, there is a clear difference in survival between the different combinations of histotypes for stages I-III. (Figures 3-6)
7. However, for stage IV, the difference between the groups is negligible after the first few years.
8. Although largest number of deaths occur in the first few years after diagnosis, late disease specific deaths still occur more than 10 years after diagnosis.[38]

Sex-cord-stromal and germ cell tumors differ from the epithelial lesions in that the overwhelming majority present in stage I. Using the SEER database, the distribution by stages for these lesions was 76.9%, 6.1%, 12.7% and 4.3%

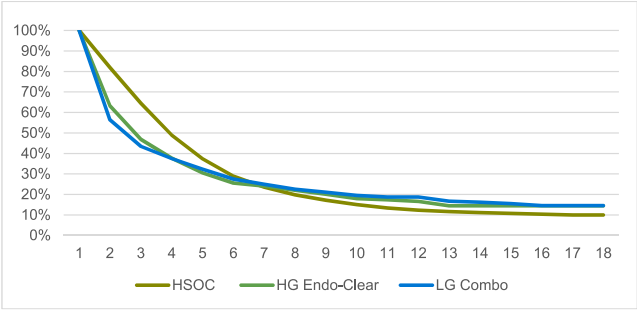

Figure 6. *Cumulative Dis Spec survival by histotype combinations stage IV.*

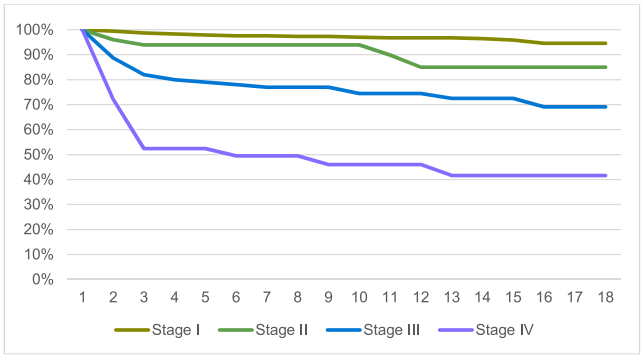

Figure 7. *Sex cord-stromal-germ cell tumors combo dis spec survival - all ages & grades.*

for stages I-IV, respectively (only 17% presenting in stages III and IV). In addition, the survival by stage was substantially better than that seen with epithelial carcinoma. This is summarized in Figures 7 and 8.[34]

Non-gestational choriocarcinoma of the ovary (not associated with a current or recent pregnancy) is a rare variant of germ cell tumors that is highly malignant and responds poorly to therapy. It tends to recur after treatment and mortality associated with the disease can be as high as 84%.[39-42]

Approximately 75% of borderline tumors of the ovary present in stage I and have a good prognosis, with a 10-year relative survival of 97%. In stages IA and IB, there is no significant increase in mortality. Survival diminishes as the stage increases but remains better than that for epithelial carcinoma at 90%, 88% and 69% 10-year survival for stages II, III and IV respectively using SEER historical data. Several clinical papers confirm the overall good prognosis. Nevertheless, there is an increase in mortality

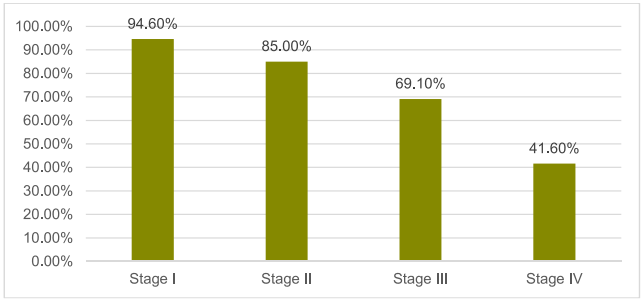

Figure 8. *Sex cord-stromal-germ cell combo Dis Spec 17 yr survival - all ages & grades.*

risk with stages other than I. The presence of different histotypes, non-invasive implants and micropapillary architecture do not affect survival. Borderline tumors are not associated with the development of other non-ovarian malignancies.[9,10,43-50]

Krukenberg tumor is a rare metastatic tumor of the ovary usually originating from the gastrointestinal tract, most often from the stomach, but also potentially representing spread from the colon or breast among other primary sites. The prognosis is generally poor with most survivals less than 2 years.[51]

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