Population-based Analysis of the Clinical Features of Primary Small Cell Carcinoma of the Ovary

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Abstract. *Background: Primary small cell carcinoma of the ovary (SCCO) is rare, making prognosis and outcomes largely undefined. Patients and Methods: Using case listing session of SEER 18 (1973-2010), we examined outcomes for patients with SCCO. Analyses were conducted with SEER*Stat 8.1.2, Microsoft Excel 2007 and GraphPad Prism 6. Comparisons were made using the Chi-square test and log-rank test (Mantel-Cox) and all p-values were 2-sided. Results: One hundred and eighty-one patients with SCCO with staging information were identified with a median age of 37 (range=10-91). Twenty-nine patients (15%) had localized, 19 (11%) regional and 133 (74%) distant disease at presentation. All patients with localized and 95% of patients with regional disease had surgery. The extent of surgery did not influence outcomes. Median overall survival (OS) varied by stage (67 months vs. 12 months vs. 9 months, p<0.001). Radiation was rarely used in localized (1 patient) or regional disease (3 patients). For comparison, 81,933 cases of SCLC were identified from the same database with a median age of 68; 8% of small cell lung cancer (SCLC) patients had localized, 29% regional and 63% distant disease. Outcomes were superior for patients with SCCO with localized disease (67 months vs. 16 months, p<0.001) but there was no clinically meaningful difference in patients with regional (12 months vs. 13 months, p=0.675) or distant disease (9 months vs. 7 months, p<0.001). Conclusion: SCCO presents at a younger age than SCLC but has a similar stage distribution. Patients with localized SCCO have a more favorable prognosis than patients with SCLC but patients with regional and distant disease have similar outcomes.*

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Small cell carcinoma of the ovary (SCCO) of hypercalcemic type (SCCOHT) is a rare tumor that most commonly affects young women at the average age of 24 (1-3). Despite being diagnosed at an early age, the tumor carries a poor prognosis due to its highly aggressive behavior (1, 3, 4).

Dickerson and his colleagues were the first to describe this malignancy in 1982. Since then, various authors have made contributions to this topic in the form of clinicopathological series and reports. Although there have been cases with favorable outcomes, the overall probability of survival is 30% for stage 1A, dropping to just 10% for more extensive disease (3, 5, 6). Rare cases, mainly focusing on only one patient as the subject, report survival over 4 years but almost all women with SCCOHT beyond stage 1A die of their disease within 1-2 years (3-5, 7).

Treatment is stage-dependent and involves surgery in the form of unilateral *vs.* bilateral salpingo-oophorectomy (BSO), chemotherapy with platinum-based regimens and sometimes radiation. However, given the rarity of this disease and, therefore, a dearth of research in this field, an effective and optimal treatment regimen has not yet been established (3, 8, 9).

Another variant of SCCO is the pulmonary type (SCCOPT), which is even rarer and affects older women with a mean age at presentation of 59. It also carries a poor prognosis with most patients dying within 1 year of diagnosis or having early recurrence. SCCOPT resembles the more commonly seen small cell lung cancer (SCLC) in histological and immunohistochemical features. A few case reports have shown that treatment for SCLC has also been successful in treating SCCOPT. Despite that, prognosis for SCCOPT remains very poor (5, 9, 10).

With only one study with over a 100 patients (4) focusing on this rare but highly aggressive cancer, our study of 181 patients aimed at analyzing the outcomes and prognosis of SCCO using the SEER database from 1973-2010. Using the same database, we looked at the data available for the much more commonly occurring SCLC and drew comparisons between the outcomes and prognosis for both entities.

Patients and Methods

We used the Surveillance, Epidemiology and End Results Program (SEER) 18 database (1973-2010) in the case listing session of SEER*Stat 8.15 to analyze the information available on SCCO and make a comparison with the data available on small cell cancer of the lung.

SEER cancer registries collect data from the states of Connecticut, Iowa, Utah, New Mexico, Hawaii and the metropolitan areas of Detroit and San Francisco-Oakland. Ten predominantly black counties from rural Georgia were also added in 1978. Other samples include American Indians residing in Arizona and native Alaskans. Los Angeles and San Jose were added in 1992 to include minority populations, especially Hispanics.

The SEER database classifies cancer histology and topography information on the basis of the third edition of the International Classification of Diseases for Oncology (ICD-O-3).

Variables set for the analysis included age at diagnosis, SEER historic stage (localized, regional or distant), treatment (surgery, radiation or both) and overall survival (OS) in months. A limitation to using the SEER database was the lack of data available on chemotherapy.

Cases were located by primary site labeled ovary (C56.9) and lung (C340-C343, C349-C349) and by histology type, including small cell and oat cell cancer (8041/3 and 8043/3). Specific codes for SCCOHT and SCCOPT were not available.

Analyses were conducted with Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.1.5 (March 31, 2014), Microsoft Excel (Redmond, Washington: Microsoft, 2007) and GraphPad Prism version 6.00 (for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com). Comparisons were made using the chi-square test and log-rank test (Mantel-Cox); all *p*-values were 2 sided.

Results

One hundred and eighty-one patients were identified with primary SCCO with staging information. These cases were collected over 37 years from 1973 to 2010. The average age at diagnosis was 37 years (range=10-91). Amongst these patients, 29 (15%) had localized disease, 19 (11%) regional and 133 (74%) distant disease. All the patients with localized disease and 95% of the patients with regional disease had undergone surgery.

Surgical options included, but were not limited to, unilateral and bilateral salpingo-oophorectomy (BSO) with or without hysterectomy (3 patients with limited disease had unspecified surgical procedures). There was no difference in outcomes for patients with localized disease whether they received a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) (11 patients) or only a BSO (15 patients) (5-year OS=60% *vs*. 62%, $p=0.283$) (Figure 1). With only 19 women with regional disease, comparisons of surgical outcomes in this sub-group were not conducted.

OS varied by stage. Patients with localized disease had an OS of 67 months compared to 12 months for regional and 9 months for distant disease ($p<0.001$) (Figure 2, Table I). The five-year OS for patients with localized disease was 52% *versus* 10% for patients with regional disease and 14% for patients with distant disease. One patient (3%) with localized disease and 3 patients (16%) with regional disease received radiation therapy as well. These numbers were too small for any conclusions to be drawn.

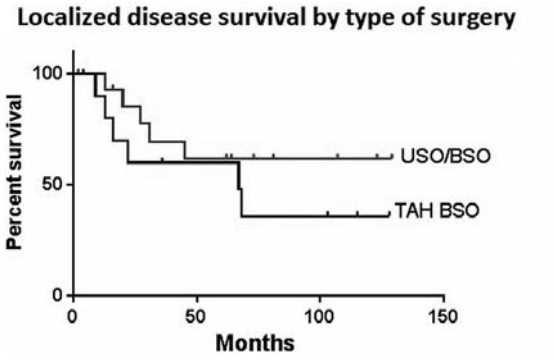


Figure 1. *Localized disease survival by type of surgery.*

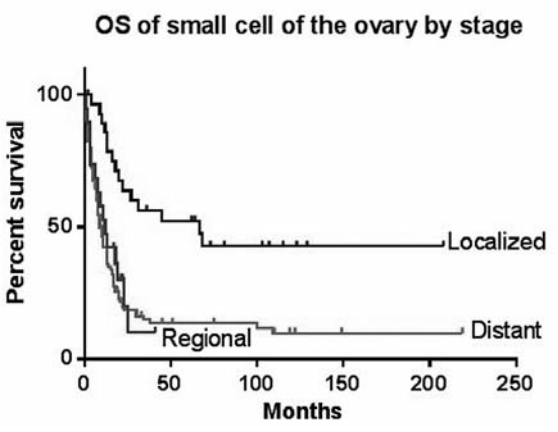


Figure 2. *OS of small cell of the ovary by stage.*

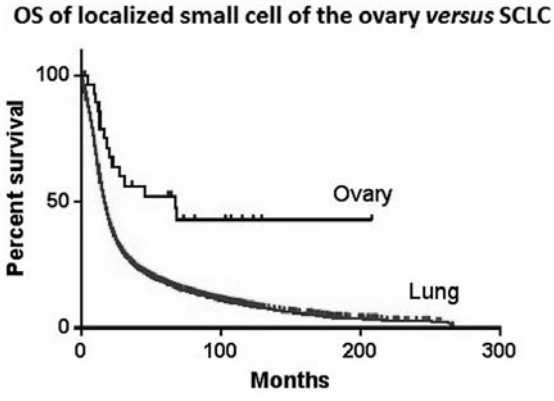
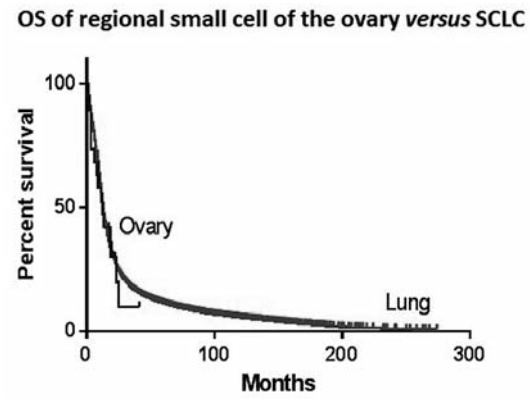


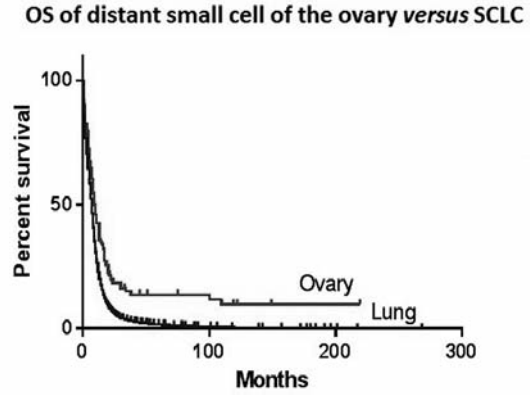
Figure 3. *OS of localized small cell of the ovary versus SCLC.*

Table I. *Comparison of disease characteristics between the small cell variant of the ovary and the lung.*

Type of cancer	SCCO	SCLC
Total number of cases	181	81.933
Average age at diagnosis	37 years	68 years
Median overall survival (OS) of localized disease	67 months	16 months
Median overall survival (OS) of regional disease	12 months	13 months
Median overall survival (OS) of distant disease	9 months	7 months
% of patients with localized disease	15%	8%
% of patients with regional disease	11%	29%
% of patients with distant disease	74%	63%



Fibure 4. *OS of regional small cell of the ovary versus SCLC.*



Fibure 5. *OS of distant small cell of the ovary versus SCLC.*

For comparison, the same database was used to identify 81,933 cases of SCLC. The median age of diagnosis for SCLC was 68 years. In the SEER database system, localized and regional disease describes limited-stage SCLC and distant disease indicates extensive SCLC. Eight percent of the patients had localized disease, whereas 29% and 63% had regional and distant disease respectively (Table I).

Outcomes were superior for patients with SCCO with localized disease compared to those with SCLC (67 months *vs*. 16 months, $p<0.001$) but OS was numerically similar for patients with regional (12 months *vs*. 13 months, $p=0.675$) and distant disease (9 months *vs*. 7 months, $p<0.001$) (Figures 3, 4 and 5).

Discussion

Utilizing the SEER database, we report on the largest experience with SCCO, to date. As other smaller reports have suggested, we found that patients with disease that had progressed beyond localized spread had dismal outcomes. Our median OS of 12 and 9 months for regional and distant disease, respectively, is consistent with the long-term survival rate of 10% reported by others (1-3, 11). While early detection seems to be the key to long-term survival, it is likely that, as for epithelial ovarian cancers, there will be no effective screening programs for SCCO (12, 13). This is evidenced by the similar stage distribution we witnessed with SCCO compared to ovarian cancer: 15% *versus* 15% localized, 11% *versus* 18% regional and 74% *versus* 61% distant at presentation (14).

Treatment consists of a multi-modality approach with surgery followed by chemotherapy and sequential or concurrent radiation therapy (11, 15, 16). Young *et al*. suggested a radical surgical approach including BSO with hysterectomy (4). That study also showed that only 7 out of most of the 150 patients had a favorable response to adjuvant chemotherapy, which consisted of various regimens, including anthracyclines, etoposide, cisplatin and alkylating agents. None of these series are large enough to define the appropriate adjuvant chemotherapy for this disease. More recent reports have shown that a fertility-sparing surgical approach followed by multi-agent chemotherapy and radiation is not inferior to the initial approach (3). This is consistent with our finding that extent of surgery did not influence outcomes. Amongst the several chemotherapy regimens used, best therapeutic results were obtained with protocols BVP (bleomycin, vinblastine, cisplatin) and BEP (bleomycin, etoposide, cisplatin). Other favorable results were obtained by alternating cycles of vinblastine, cisplatin, bleomycin with cycles of cyclophosphamide, doxorubicin and etoposide or a protocol combining induction with BEP followed by consolidation with vincristine, actinomycin D and cyclophosphamide (VAC) (3, 9-11, 16). Radiotherapy, after or with chemotherapy, was common in all patients with long-term survival (3, 9).

Our results are consistent with the given literature when it comes to describing the aggressive nature of this rare tumor. Seventy-four percent of our population had distant disease

at presentation. Patients with regional disease survived a median of 12 months and those with distant disease survived a median of 9 months. Harrison *et al*. looked at the results of five studies on SCCO and summarized OS based on stage (3). Those results showed a 13-month median survival for patients with stage III and 7-month median survival for patients with stage IV disease. In his own subject population, he reported an OS of 6 months for patients with stage III disease. Our findings are consistent with these demonstrating that patients with regional or distant SCCO have dismal outcomes.

The median OS for patients with localized disease in our population was 67 months. This was significantly higher than, but is consistent with, the trends of what has been previously reported. Harrison *et al*. reported an OS of 40 months for stage I, which was also significantly higher than the 18 months reported in his summary of previous literature.

Compared to ovarian cancer, SCCO carries a markedly inferior 5-year survival by stage: 92% *versus* 52% for localized, 72% *versus* 10% for regional and 27% *versus* 14% for distant disease (14). Overall, the behavior of SCCO was more similar to that of SCLC rather than ovarian cancer.

Our database did not provide information on chemotherapy as part of the treatment strategy. This was one of the limitations we faced and, therefore, had to draw comparisons based on surgery and radiotherapy being used as treatment options. Studies, which looked at surgery, chemotherapy and radiation as treatment modalities, concluded that surgery was the primary option for early disease (1, 3, 4). Our lack of data on chemotherapy did not let us draw this conclusion.

Emphasis has been laid on the role of radiation in the long-term survival of these patients. Radiation therapy was given to only 1 patient with localized disease, 3 patients with regional disease and 12 patients with distant disease. Out of the 12 patients with distant disease receiving radiotherapy, only 2 had an OS of 22 months. The rest were not reported to have an OS of greater than 12 months. Other studies mentioning the improved OS with radiation had a small sample population. Our study population is the largest one to date. This is the biggest strength of our study and, even though 181 patients is still not a large enough sample to draw definitive concrete conclusions, we believe that our results will make important contributions to the already existing excellent but limited studies on this disease.

We also analyzed 81,933 cases of SCLC to draw a comparison in the OS by stage. We saw that patients with SCCO localized disease had superior outcomes when compared to patients with SCLC localized disease. Regional and distant disease had similar outcomes in both entities.

SCLC accounts for 15-20% of all lung cancers. Cigarette smoking has been established as the most important cause of SCLC accounting for nearly 95% of the cases. Recent trends in smoking along with a change of cigarette composition with decreased tar and nicotine have contributed to a decline in the incidence of SCLC (17-20). The association of smoking with ovarian cancer varies across the histological type and the strength of that association is moderate. Literature has shown a moderately increased risk of invasive and borderline mucinous tumors and borderline serous tumors of the ovary with cigarette smoking (21).

Tobacco smoking exerts its carcinogenic effect through more than 60 mutagens that bind to and chemically mutate DNA. The DNA damage produced by years of tobacco smoking causes the genetic changes associated with lung cancer (22, 23). Whereas the role of smoking in determining the behavior of SCLC has clearly been established, the role of smoking in SCCO has not been explored in detail. Germline and somatic inactivating mutations in SMARCA4 have recently been implicated in the oncogenesis of SCCO (22, 24, 25). Current literature, however, does not comment on the effect of cigarette smoking on SCCO. Whether or not the difference in outcome for localized SCCO and SCLC can be attributed to tobacco use is not clear. Further studies to determine the association of smoking with SCCO will help us in delineating the difference in the outcomes of the two entities.

Although SCLC is highly sensitive to chemotherapy and radiation initially, it is still a therapeutic challenge (17-19). Similar to SCCO, treatment depends on the stage of the disease. With advancements made in the past years, the 5-year survival rate for localized disease has been around 15-25%. Extensive-stage disease, on the other hand, carries a 5-year survival of less than 1 % (17-20, 26, 27).

Conclusion

In summary, primary SCCO is rare, which presents challenges for diagnosis, prediction of outcomes and overall treatment strategies. Based on this SEER database analysis, SCCO has a more favorable prognosis than SCLC in localized malignancy. Literature available is not sufficient enough to guide us with an exact treatment protocol. Surgery has been shown to be the primary treatment modality in early disease. As per literature, multi-agent chemotherapy regimens have been shown to work in some instances. Concurrent or sequential radiation has also improved OS. Our study was not able to verify the benefit of radiation on the long-term survival of these patients. Despite that, SCCO remains a challenge and further clinical studies are warranted to help overcome it.

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