

Small cell of the ovary, hypercalcemic type—Analysis of combined experience and recommendation for management. A GCIG study

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Abstract

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare tumor typically affecting young women. It is an aggressive malignancy with a poor prognosis and few long-term survivors.

Objective. Investigate the outcome of patients with SCCOHT.

Method. Data were collected for patients with SCCOHT treated in Australia, Canada and Europe. Information included stage, surgery, chemotherapy, radiotherapy, recurrence and survival.

Results. The median follow-up is 13 months for all patients and 35.5 months in surviving patients. Ten patients had FIGO stage I tumors, six stage III tumors and one stage unknown. All underwent surgical resection. Adjuvant platinum-based chemotherapy was given to all patients. Seven received adjuvant radiotherapy with either pelvic and para-aortic radiotherapy, average dose 46.5 Gy (40 Gy/25#–50.4 Gy/23#), or pelvic and whole abdominal radiotherapy, average dose 45 Gy to pelvis and 25 Gy (22.5 Gy/22#–30 Gy/25#) to abdomen.

The median survival for stage I tumors was not reached and was 6 months for stage III tumors. For the ten patients with stage I tumors: six received adjuvant radiotherapy with five alive and disease-free; four received no adjuvant radiotherapy with one alive and disease-free, while three have relapsed with one alive and disease-free after resection. Of the seven patients with stage III or unknown stage tumors, all but one have died. Recurrences were most frequent in the pelvis and the abdomen. Patients receiving salvage treatment with chemotherapy and radiotherapy did poorly.

Conclusion. We advocate a multi-modality treatment approach including surgery, chemotherapy with the addition of radiotherapy either sequentially or concurrently.

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Keyword: Small cell carcinoma of the ovary; Hypercalcemic type

Introduction

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is a rare tumor that typically affects young women, with hypercalcemia often, but not necessarily always present at

diagnosis [1,2]. Since Dickersin identified this tumor as a unique entity in 1982, there have been a number of additional clinico-pathological series and case reports that have described the pathology and clinical behavior as well as prognosis which has generally been reported to be poor [3–6]. Although there is evidence of benefit and response to platinum-based chemotherapy and radiotherapy, the majority of patients reported in the literature have relapsed despite aggressive multi-modality

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treatment, and the optimal approach to management is unknown.

The histogenesis of SCCOHT and the mechanism of the development of the hypercalcemia are unknown. Young et al. originally suggested that these tumors had an epithelial origin on the basis of immunohistochemical (IHC) staining and electron microscopy findings of abundant dilated rough endoplasmic reticulum [2]. A primitive germ cell origin has also been postulated [7]. However, others have reported on the basis of immunohistochemical and ultrastructural features and findings on comparative genomic hybridization that it is neither a germ cell nor epithelial origin, and the histogenesis is still unknown [8–10].

SCCOHT differs markedly in clinical presentation, light and electron microscopic (EM) examination, IMC staining and ultrastructural features from small cell undifferentiated/neuroendocrine carcinoma of the lung and extrapulmonary sites. Microscopically, small cell carcinomas of the lung demonstrate ovoid-to-angulated nuclei with nuclear molding, evenly dispersed nuclear chromatin and inconspicuous nucleoli [11]. IHC demonstrates epithelial membrane antigen in most cases [13], and vimentin staining is absent [14]. EM shows neuroendocrine differentiation, with dense core neurosecretory granules in some of the cells. In contrast, the ovarian small cell cancers have irregularly clumped nuclear chromatin with small but readily discernible nucleoli [12]. Prominent areas of crush artifact are not features of ovarian small cell carcinoma. On IHC, epithelial membrane antigen is positive in only one third, and vimentin is positive in up to approximately 50% [10]. Interestingly, in the original description, five of seven tumors investigated by IHC showed positive staining for parathyroid-hormone-related protein [2]. EM reveals abundant rough endoplasmic reticulum, a feature not seen in the lung and other extrapulmonary small cell tumors [12].

It should be noted that primary neuroendocrine small cell carcinomas of the ovary are a quite different and distinct entity. Eichhorn et al. reported 11 of cases of the pulmonary type of small cell carcinoma of the ovary, which occurred in menopausal and postmenopausal women, and had histologic and immunohistochemical features similar to those of the more common pulmonary small cell carcinoma and can be distinguished from the SCCOHT even when the tumor is confined to the ovary [15]. There are a number of other tumors which could also be confused with SCCOHT including granulosa cell tumors, lymphomas, primitive neuroectodermal tumors, melanoma, metastatic round cell sarcomas, small cell desmoplastic tumors and possibly even dysgerminomas [16]. All of these have distinctive morphologic, immunohistochemical and clinical features and should not be confused with SCCOHT.

There has been general agreement that SCCOHT are aggressive malignancies with a poor prognosis. Although there have been several reports in the literature of patients with prolonged survival [17,18], the majority of patients have died within 1–2 years of diagnosis [1–4,19,20]. It is not possible to draw conclusions as to what constitutes the optimal approach to treatment or what is the best chemotherapy regimen. No prospective studies have been performed and nor are such studies likely given the relative rarity of these tumors, and

treatment decisions have been based on our knowledge of the aggressive nature of this disease and from small series and reports. We have sought to expand on the current literature by collating the experience of treating SCCOHT from a number of member institutions of the Gynaecological Cancer Intergroup (GCIG) in an effort to better understand the clinical features, response to treatment and outcome so we can design more rational approaches to management.

Methods

A survey was sent to members of the GCIG requesting data on patients with SCCOHT to allow us to better characterize the prognosis and approach to treatment. Data which were collected included: age, symptoms at diagnosis, presence of hypercalcemia, FIGO stage, surgery, chemotherapy and radiotherapy, response to treatment, site of recurrence, progression, overall survival and salvage treatments. Specific details of chemotherapy regimens and radiation protocols were sought. While it would have been ideal to have reviewed all the pathology centrally, this was not possible. However, it should be noted that all patients had their pathology reviewed by gynecologic pathologists at individual centers, and, in many instances, the pathology was reviewed by a number of gynecologic pathologists. Ethics approval for data collection and analysis was obtained from Prince of Wales Hospital Sydney, Australia.

Results

A total 17 patients were included in this analysis. Cases were collected over 15 years from April 1989 to May 2004. The average age at diagnosis was 34.5 years (range 24–71 years). The median follow-up was 13 months (range 2–71 months) for all patients and 35.5 months (range 8–71 months) in surviving patients. Four patients surviving greater than 5 years were no longer being routinely followed.

The most common presenting symptoms included pain (53%), abdominal swelling or bloating (41%), urinary frequency (17.6%), fatigue (11.8%), vomiting (11.8%), dyspareunia (11.8%) and change in bowel pattern (11.8%). Three patients (17.6%) were asymptomatic. Hypercalcemia was not routinely tested at initial presentation as the diagnosis was not suspected, and results were recorded in only ten patients preoperatively. Four of these patients were hypercalcemic, two with symptoms attributable to hypercalcemia, and two were asymptomatic.

Surgery

The type of surgery undertaken is detailed in Table 1. Ten tumors were FIGO stage I (58.8%), six (35.3%) were stage III, and, in one patient, the stage was unknown. Staging is reported as per the referral center. Three patients' tumors were initially staged as IC by surgeons at peripheral centers, but, at further surgery, 2 patients were upstaged to stage III and 1 patient was upstaged on CT scanning.

Full staging laparotomies including hysterectomy and bilateral salpingo-oophorectomy were performed in 8 patients (47.1%), while 8 patients (47.1%) had more limited surgery. The extent of surgery was unknown in 1 patient. Optimal debulking was recorded for 13 patients (76.5%) with <1 cm residual disease. One patient had 1–2 cm residual disease, two

Table 1
Treatment and outcome in current series

Age	Stage	Surgery	Residual	Chemotherapy	Radiotherapy	Outcome
33	I	O	<1 cm	BEP	No (refused)	Alive without disease 10 months
33	IA	Hyst and BSO	<1 cm	Cis/Etop	45 Gy Pel/PA	Alive without disease 60 months ^a
37	IC	SO	<1 cm	BEP	30 Gy WA and 45 Gy Pel	Alive without disease 51 months
25	IC	O	<1 cm	Cycl/Epi/Cis	No	Recurrence 10 months after diagnosis Surgery and Radiotherapy CR POMB-ACE on progression PR Tax PD, Ifos PD. Died of disease 29 months
28	IC	O and Om	<1 cm	Cis/Etop and Carb/Tax	No	Recurrence 9 months after diagnosis Surgery with complete resection Alive without disease 16 months
34	IC	Hyst, BSO and Om	<1 cm	Cis/Etop	22.5 Gy WA and 45 Gy Pel	Alive without disease 71 months ^a
30	IC	SO	<1 cm	GOSMCC2	40 Gy Pel/PA	Alive without disease 59 months ^a
35	IC	Hyst, BSO, Om and NS	<1 cm	Cis/Etop	22.5 Gy WA and 45 Gy Pel	Alive without disease 65 months ^a
40	IC	Hyst and O ^b	>2 cm	SMCC2	50.4 Gy Pel/PA	Alive with disease 8 months
25	IC ^c	O (perforation)	<1 cm	Carb/Tax	No	Recurrence 9 months after diagnosis Complete resection, recurred after 2 months Surgery, radiotherapy and Cis Progression treated with Etop PD, Doxil Alive with disease 16 months
24	III	O, B	>2 cm	BEP + Carb/Taxol	No	Stable disease with chemotherapy Radiotherapy with disease progression Died of disease 6 months
29	IC ^d IIIC	C-sect, SO and B (iatrogenic tumor rupture) TAH, Om, NS	<1 cm	Carb/Tax	No	Recurrence 7 months after diagnosis Topo PD, Etop PD. Died of disease 11 months
36	I ^c IIIC	O (piecemeal)	<1 cm >5 cm	Cis/Etop	50.4 Gy Pel/PA	Rapid progression after initial surgery Complete response to chemotherapy Alive without disease 5 months
31	IIIB	Hyst, BSO, Om	<1 cm	Cis/Etop	No	Recurrence 6 months after diagnosis No salvage treatment. Died of disease 7 months
48	IIIB	Hyst, BSO, Om and NS	<1 cm	Carb/Tax	No	Progressed on chemotherapy after 2 cycles No salvage treatment. Died of disease 3 months
71	IIIC	Hyst, BSO and Om	>1 cm	Carb	No	Recurrence 9 months after diagnosis Carb PD, Palliative colostomy. Died of disease 13 months
27	NR	Not given	NR	Carb/Tax	No	Progressed on chemotherapy after 2 cycles Died of disease and sepsis 2 months

Surgery: O, oophorectomy; SO, salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy; Hyst, hysterectomy; Om, omentectomy; NS, node sampling; C-sect, cesarean section; B, biopsy; NR, not reported.

Chemotherapy: BEP, bleomycin, etoposide and cisplatin; Cis, cisplatin; Etop, etoposide; Cycl, cyclophosphamide; Carb, carboplatin; Tax, paclitaxel; Ifos, ifosfamide; Topo, topotecan; GOSMCC2, cisplatin, paclitaxel, etoposide and carboplatin; SMCC2, cisplatin, paclitaxel, etoposide and carboplatin; POMB-ACE, cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide.

Radiotherapy: Pel, Pelvis; PA, para-aortic nodes; WA, whole abdomen.

Response: PR, partial response; CR, complete response; PD, progressive disease.

^a No ongoing follow up.

^b 1 patient previous oophorectomy.

^c Outside staging IC, restaged IC at referral center 1 month later.

^d Outside staging IC, restaged IIIC at referral center 2 months later.

^e Outside staging I, restaged IIIC at referral center 1 month later.

patients had >2 cm residual disease, and, in the other, this was not reported.

Outcome based on stage

Of the ten patients with FIGO stage I disease, the median follow-up was 40 months (8–71 months). Initial surgery in six patients involved conservation of the uterus and contra-

lateral ovary, while the other four patients underwent full surgical staging including total abdominal hysterectomy and bilateral salpingo-oophorectomy. At last follow-up, seven patients are alive and well without evidence of recurrence, and three have relapsed. All three were treated with surgery on recurrence, and 2 patients received radiotherapy and chemotherapy. One patient remains disease-free at 16 months after surgery alone.

Six patients had FIGO stage III disease, and, in one patient, the stage was not known. All but one underwent complete surgical staging and tumor debulking. Median survival was 6 months (range 2–13 months). Recurrences occurred during or soon after completing adjuvant chemotherapy. Only one patient with stage III disease is alive without recurrence, 6 months after the completion of chemotherapy and radiotherapy.

Chemotherapy

Adjuvant chemotherapy was given to all patients as detailed in Table 1. Performance status prior to chemotherapy was documented in fifteen patients. Twelve patients were ECOG 0–1, and three patients were ECOG 2–4. After 1996, paclitaxel was incorporated into several chemotherapy regimens.

Eight patients received cisplatin and etoposide with or without bleomycin. Five had radiotherapy after the completion of chemotherapy. Of the five stage I patients, all were currently alive and disease-free at last follow-up including four long-term survivors greater than 50 months. Of the three patients with stage III disease treated with cisplatin and etoposide, one is alive without disease at 6 months (also received radiotherapy), and the other 2 died after 6 and 7 months.

Four patients were treated with carboplatin and paclitaxel. One patient had stage IC cancer, and she recurred after 9 months. Of the three patients with stage III cancer and stage unknown, two progressed during chemotherapy and the other recurred after 7 months.

Three patients were treated with a combination including: cisplatin, etoposide, paclitaxel and carboplatin. All these patients had stage IC disease, and two received concurrent radiotherapy. In the patient with measurable disease, there was a partial response. The other two patients were alive and free of disease at last follow-up of 16 and 59 months. The remaining two patients were treated with cisplatin, adriamycin and cyclophosphamide or single agent carboplatin, and both have relapsed within a short period.

Salvage chemotherapy was used in four patients with little benefit. Multiple agents were trialed and in most cases administered as single agents. The only regimen where a response was reported was with POMB-ACE after two cycles (patient 4). Significant toxicity was reported, and the response was short-lived with progression after the fourth cycle of treatment.

Radiotherapy

Adjuvant radiotherapy was given to seven patients as detailed in Table 1. All patients completed treatment. Six patients had stage IC cancer, while the other patient had stage IIC. Four patients received pelvic and para-aortic radiotherapy. The average dose was 46.5 Gy (40 Gy/25#–50.4 Gy/23#). In 2 patients, this was given concurrently with cisplatin as part of their protocol, each after 6 weeks of combination chemotherapy.

The second approach used in three patients was whole abdominal RT with a pelvic boost. The average dose to the abdomen was 25 Gy (22.5 Gy/22#–30 Gy/25#) and to the

pelvis 45 Gy in 32#. Radiotherapy in these patients was scheduled after the completion of chemotherapy.

In the seven patients who received radiotherapy, five are long-term survivors greater than 50 months. Only one patient with stage III disease received radiotherapy, and she remains well, but follow-up is short at 6 months after completion of therapy. Only one patient who received radiotherapy has relapsed.

Of the patients who did not receive radiotherapy, three of four with stage I tumors had recurrences, and one is alive without disease at 10 months. Five of six with stage III or not reported have died, and the other is alive without disease at 5 months. The median survival is 11 months (range 2–29 months). Three patients had palliative radiotherapy at relapse, however, duration of benefit was limited, and all patients have since died of disease.

Pattern of recurrence

Eight patients recurred after initial surgery and adjuvant treatment. The sites included: pelvis (6 patients), abdomen (4 patients), small bowel mesentery (1 patient), retroperitoneal nodes (1 patient), ascites (1 patient), pleural effusion (1 patient) and supraclavicular node (1 patient). Four patients had an elevated serum calcium at time of recurrence.

Discussion

The prognosis for patients with SCCOHT is generally believed to be poor, and treatment approaches have included surgery usually followed by adjuvant chemotherapy, radiotherapy or both. The clinico-pathological studies, which have been reported, have largely focused on the histopathological features and prognosis. There have been relatively few clinical studies reported in the literature, and they mainly consist of small cases series and single patient case reports.

The optimal surgical approach is unknown, but, as the disease is unilateral in 99% of cases, it seems unnecessary to perform a bilateral salpingo-oophorectomy and hysterectomy in this generally young population, and unilateral oophorectomy is a reasonable option [2,20,21]. There are no reports of subsequent pregnancy following fertility sparing surgery, but, given that many patients have received a combination of chemotherapy and/or radiotherapy, this is not surprising [1–6]. It is difficult to advocate transposition of the remaining ovary in young women if whole abdominal radiotherapy is to be used as part of the treatment plan.

The largest pathological series reported by Young [2] included 150 patients, of whom 50% had stage I, 5% stage II, 43% stage III and 1% stage IV disease. These patients were referral cases for pathology review and were accrued over many years, and treatment details are few. It is likely that many would have had incomplete staging procedures and a substantial number of patients may have been under-staged. Of the 50 patients with apparent stage IA tumors, 33% were alive and disease-free with an average follow-up of 5 years. Very few patients with a higher stage disease survived, and, in his series, only 10% with stage IC and 6.5% of patients with stage II, III and IV small cell ovarian cancer were long-term survivors.

Features associated with a more favorable survival in patients with stage IA tumors included: age >30, a normal pre-operative calcium, tumor size <10 cm and the absence of large cells [2]. While there was a trend for improved outcome with more extensive surgery in the patients with stage IA disease, the impact of this on overall survival is a matter of conjecture.

The role of adjuvant chemotherapy and radiotherapy was unclear from the large series reported by Young et al. [2]. The majority of patients received some form of additional treatment, generally chemotherapy, but some also received radiotherapy or both modalities. The benefit and impact of chemotherapy were difficult to interpret as a variety of regimens were used, but the authors suggested that there was no apparent benefit in patients with stage IA disease. Interestingly, there was an improved outcome in the 5 patients receiving adjuvant radiotherapy with 4 of these patients surviving [2].

In the series by Dickersin, which included 11 new cases, four patients received chemotherapy as adjuvant treatment and in four patients following relapse. There was little evidence of response in patients with measurable disease, and all patients died. In one patient with peritoneal spread at time of surgery, radiotherapy contributed to her survival of 5 years prior to subsequent relapse [1].

Seidman reviewed 20 cases, however, clinical data were incomplete with clinical follow-up in 16 patients and information on post-operative treatment in 11 patients. Ten patients received chemotherapy (one at relapse), and three received radiotherapy (one at relapse). Only six patients received chemotherapy incorporating cisplatin. The median survival was 13 months with 11 patients dying within 2 years. There was only one long-term survivor [6].

Several smaller series have been published. Combination platinum-based chemotherapy was used for most patients, with few receiving adjuvant radiotherapy. Toxicity was considerable with VCPBAE [5]. Overall, most patients relapsed soon after

treatment, and their disease followed an aggressive course with few long-term survivors [3–5,18]. A summary of outcomes based on stage at diagnosis and treatment is presented in Table 2 and includes series where data could be extracted from the literature.

In our series, the overall survival of patients with stage I disease was significantly higher than that reported in other series, with 7 of 10 patients alive without disease at a median follow-up of 40 months and with five long-term survivors. The patients with more advanced disease generally had a poor prognosis, in keeping with the reported experience, although it should be noted that there are reports of a small number of long-term survivors among patients with more advanced disease, and 1 of the patients with stage IIIC disease in our series remains free of disease, but follow-up is still short.

There are several possible explanations to account for our better results. This is a retrospective series with cases referred from a number of centers, and this may have led to selection bias in the cases that we received. However, this is an unlikely explanation as all patients identified on departmental databases were included. All our patients were treated at gynecological cancer treatment centers, and the majority had full surgical staging, which could account for the better outcomes in patients with stage I disease in this series. Three patients were initially treated at peripheral centers, and either had inadequate staging or iatrogenic tumor spillage at time of their initial surgery which may have contributed to the poor outcome in these patients. This highlights the need for these women to be referred to specialist gynecology oncologists and centers able to provide full multi-disciplinary care.

Adjuvant chemotherapy differed, but all patients had platinum-based chemotherapy. The long-term survivors in our series all received chemotherapy incorporating cisplatin and etoposide. It is not possible to say that this was superior to carboplatin and paclitaxel as the patients receiving the latter

Table 2
Survival based on stage of disease

No.	Stage	Surgery	Chemotherapy	Radiotherapy	Survival	Outcome
<i>Summary from the literature^a</i>						
18	IA–IC	9 CSL 8 Limited	9 patients	4 patients	MS 18 months 5–58 months	6 A + W 1 AWD 11 D
7	IIB–IIC	1 CSL 4 Limited	5 patients	3 patients	MS 9 months 7–66 months	2 AWD 5 D
6	IIIA–IIIC	5 CSL 3 Limited	6 patients	1 patient	MS 13 months 4–23 months	6 D
1	IV	1 CSL	1 patient	0 patient	7 months	1 D
<i>Current series</i>						
10	IA–IC	3 CSL 7 Limited	10 patients	6 patients	MS 40 months 8–71 months	7 A + W 2 AWD 1 D
7	IIIA–IIIC Unknown	4 CSL 2 Limited 1 Unknown	7 patients	1 patient	MS 6 months 2–13 months	1 A + W 6 D

CSL, Complete staging laparotomy including hysterectomy and bilateral salpingo-oophorectomy; Limited, Less than complete staging laparotomy with conservation of uterus or ovary; MS, median survival; A + W, alive and well; AWD, alive with disease; D, deceased.

^a Dickersin [1], Ablar [4], Senekjian [5], Peccatori [18], Hamilton [3].

combination had more advanced disease. However, in the patients receiving carboplatin and paclitaxel, two progressed during treatment and the other two soon after completion of treatment. It is notable that, in one patient with bulky disease, a complete response was seen with cisplatin and etoposide.

The most striking difference was the use of radiotherapy in this series of patients. In our patients, most of the long-term survivors received adjuvant radiotherapy either following or concurrently with chemotherapy. In the series by Young, a benefit for radiotherapy contributing to survival was postulated with four of five patient's long-term survivors having had radiotherapy [2]. Additionally, in the series by Dickersin, their 5-year survivor received adjuvant radiotherapy to the abdomen. In the other reported series, the use of adjuvant radiotherapy was used alone which differs from our series [1].

The pelvis and the abdomen were the two most common sites of relapse. Given the pattern of peritoneal spread with positive washings in most patients at diagnosis and the sites of recurrence in those not receiving radiotherapy, whole abdominal radiotherapy may be preferable to pelvic radiotherapy alone. However, with small numbers, a definitive recommendation is not possible. It is difficult to know whether the superior survival outcome in our patients was due to the combination of chemotherapy and radiotherapy or due to effect of the radiotherapy alone.

Patients were treated over a 15-year period. Extent of surgery was individualized, and complete debulking was attempted in all patients, with conservation surgery used in some women with stage I disease at laparotomy. There was no significant change in surgical approach over this period. The main change to treatment was the incorporation of paclitaxel into several adjuvant chemotherapy regimens from 1996. Radiotherapy was used throughout this time period, principally in patients with stage I disease. It is unlikely that patient outcomes were altered as a result of the availability of new treatments over time, with all the long-term survivors (>5 years) receiving treatment prior to 2001.

In summary, we advocate a multi-modality treatment approach including surgery to fully stage extent of disease followed by chemotherapy with a combination including cisplatin and etoposide. We advocate the addition of radiotherapy either sequentially or concurrently. Given the apparent superiority of the concurrent approach, in other tumor types, albeit with the potential for added toxicity, we plan to develop a protocol and make it available on the GCIG rare tumor website.

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