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ORIGINAL ARTICLE

Retrospective Cohort Study

# Clinical benefit and tolerability of adjuvant intraperitoneal chemotherapy in patients who have or have not received neoadjuvant chemotherapy for advanced ovarian cancer

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## Abstract

*BACKGROUND*

Adjuvant chemotherapy using intraperitoneal (IP) treatment has demonstrated survival benefit over intravenous (IV) therapy alone in patients treated with upfront debulking surgery for advanced stage ovarian cancer. Neoadjuvant chemotherapy followed by interim surgery and adjuvant chemotherapy has similar outcome in survival as compared to upfront surgery followed by adjuvant IV chemotherapy. IP chemotherapy has not been widely adopted in clinical practice for a number of reasons. Whether IP chemotherapy delivered in the patients who received neoadjuvant chemotherapy can be well tolerated or confers any clinical benefit has not been well studied.

*AIM*

To evaluate the experience of adjuvant IP chemotherapy in the community cancer clinic setting, and the clinical benefit and tolerability of incorporating IP chemotherapy in patients who received neoadjuvant treatment.

*METHODS*

We retrospectively evaluated toxicities and outcomes of patients with stage III and IV ovarian cancer diagnosed at our institution between 07/2007 and 07/2015 who received intraperitoneal chemotherapy after cytoreductive surgery (group 1) or after neoadjuvant chemotherapy followed by interim surgery (group 2).

*RESULTS*

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Thirty eight patients were treated with IP chemotherapy, median age was 54 years old (range 38.6 to 71 years). In group 1 ($n$ = 25), 12 (48%) of the patients completed 4 or more cycle of IP treatment after upfront debulking surgery; while in group 2 ($n$ = 13), 8 (61.5%) of the patients completed all 3 cycles of the assigned IP chemotherapy after receiving neoadjuvant IV chemotherapy followed by surgery, and 2 (15.4%) more patients tolerated more than 3 cycles. In those patients who did not get planned IP chemotherapy, most of them were treated with substitutional IV chemotherapy, and the completion rate for 6 cycles of IV + IP was 92%. Abdominal pain, (64% in group 1 and 38% in group 2), vomiting, (36% in group 1 and 30.8% in group 2), dehydration (16% in group 1 and 15.4% in group 2), and hypomagnesemia (12% in group 1 and 15.4% in group 2) were the most common adverse effects in all patients, while patients who have received neoadjuvant chemotherapy were more likely to get hypokalemia, fatigue and renal insufficiency. Progression free survival (PFS) was 26.5 mo (95% CI 14.9, 38.0) in group 1 and 27.6 mo (95% CI 13.1, 42.1) in group 2. The overall survival was 100.2 mo (95% CI 67.9, 132.5) for group 1 and 68.2 mo (95% CI 32.2, 104.0) for group 2. For the entire cohort, PFS was 26.5 mo (95% CI 15.9, 37.0) and OS was 78.8 mo (95% CI 52.3, 105.4).

*CONCLUSION*
The use of IP/IV chemotherapy can be safely administrated in the community cancer clinic setting. The use of IP/IV chemotherapy in patients who have received neoadjuvant chemotherapy followed by surgery is feasible and tolerable. Despite various modification of the IP regimen, incorporation of IP chemotherapy in the adjuvant setting appears to be associated with improved PFS and overall survival.

**Key words:** : Ovarian cancer; Intraperitoneal chemotherapy; Community setting; Safety; Tolerability; Outcome



**Core tip:** Intraperitoneal chemotherapy has shown survival benefits in the adjuvant setting among the patients with advanced stage ovarian carcinoma undergoing debunking surgery. However, this intraperitoneal route could not be widely adopted due to a number of issues including patients choice and its cumbersome nature. The present study explores its feasibility in a community cancer setting. We have retrospectively analyzed the rates of toxicities and outcome of the patients who received this therapy in our cancer center. We conclude that intraperitoneal chemotherapy can be safely administered in the community cancer setting and improves the overall and progression free survival.

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## INTRODUCTION

Epithelial ovarian cancer is the most common cause of death among women with gynecologic malignancies and the 5th leading cause of cancer death in the United States[1]. Approximately 75% of women have stage III or IV disease at diagnosis[2]. Several randomized studies have demonstrated survival benefit when intraperitoneal (IP) chemotherapy is utilized in the adjuvant treatment after maximal debulking surgery *vs* only intravenous (IV) chemotherapy[3-5]. Cochrane review of 8 IP studies showed a hazard ratio (HR) of 0.81 to be less likely to die from ovarian cancer after receiving IP *vs* IV alone[6]. Another long term follow up study using combined data from Gynecologic Oncology Group (GOG) 114 and GOG 172 demonstrated median survival difference of about 10 mo in favor of IP therapy[7]. However, IP

chemotherapy has not been widely used in the academic or community cancer centers alike, due to concerns of toxicity, such as abdominal pain, severe nausea and vomiting, catheter associated infection, as well as unfamiliarity of the treatment or unavailability in the facilities[8]. In a retrospective examination of six medical centers in the National Comprehensive Cancer Network, the use of IP was found in up to 50% of the eligible patients which peaked in year 2007-2008, but the usage rate plateaued afterwards[8]. More recently, alternative IV regimens incorporating dose dense delivery of paclitaxel or angiogenesis inhibitor bevacizumab have been reported and have been applied in the clinical practice[9-11].

European Organization for Research on Treatment of Cancer (EORTC) conducted a randomized study comparing neoadjuvant IV chemotherapy followed by interim debulking surgery followed by adjuvant chemotherapy *vs* upfront debulking surgery followed by adjuvant IV chemotherapy, and showed that the neoadjuvant approach is not inferior to the adjuvant IV treatment[12]. The question then emerges whether patients who have received neoadjuvant IV chemotherapy followed by optimal debulking surgery can still tolerate and benefit from adjuvant IP chemotherapy. An OV21/PETROC study tried to address this question. The first report of the phase II portion did show a lower progression rate at 9 mo as compared to IV chemotherapy suggesting benefit of IP chemotherapy after neoadjuvant treatment[13].

Our community cancer center has started offering IP chemotherapy to eligible ovarian cancer patients since 2005. Since 2010, after the publication of the EORTC study using the neoadjuvant chemotherapy approach, we continued to offer adjuvant IP chemotherapy in patients who received neoadjuvant chemotherapy. In this study, we aimed to examine the experience of conducting IP chemotherapy in a community cancer center setting. We will compare the toxicity profile of IP when used after upfront surgery versus after neoadjuvant chemotherapy and interim debulking surgery, and evaluate the outcomes of patients who received IP treatment either after upfront surgery or after neoadjuvant treatment.

## MATERIALS AND METHODS

This study was reviewed and approved by the Institutional Review Board. The electronic medical records and hospital tumor registry was queried for all patients who were diagnosed with ovarian, fallopian tube, or primary peritoneal cancer based on the International Classification of Diseases (ICD) 9 and ICD 10 codes. Patients who were diagnosed of stage II, III or IV cancers between July 2005 and July 2015 and received at least 1 treatment of IP chemotherapy were eligible and included in the analysis. Medical records were reviewed for collection of data on demographics, pathology, chemotherapy agents, regimens, dose modifications and side effects. The progression free survival (PFS) and overall survival (OS) were calculated using the day of surgery as the start day, and March 30, 2017 as the last day of censor.

PFS was considered to have ended at the time of cancer progression as shown on radiography, or death from any cause. If progression was first detected on the basis of increased CA125 level, and a computed tomography (CT) scan was performed within 4 wk, then the date of progression would be the date of the scan. If no CT scan was done within 4 wk, then the date of CA125 increase, with levels defined by the Gynecologic Cancer Intergroup criteria[14], would be the date of progression. If a patient was lost for follow up, then the last day of follow up will be the end date for calculation of PFS or OS. In a small number of patients who were lost for follow up and had Medicare insurance, the Medicare data base was checked to estimate the date of death.

Patients treated with IP chemotherapy following surgery for recurrence disease were included. In PFS and OS calculation, the start day was the day of the second surgery.

We hypothesized that IP chemotherapy would be associated with improved survival compared with IV chemotherapy, and our pre-study statistical sample size calculation indicated that at 31 patients will be required to have 80% power to compare to the historical data, assuming a median OS of 30 mo in the primary surgery group[12], and 60 mo for the IP group[7], with SD of 60 and the effect size of 0.5. Kaplan Meier estimation curves were used for estimation of survival and log-rank test was applied. Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) was used for all the calculations.

## RESULTS

### Patient characteristics

Between July 2005 and July 2015, 63 patients were diagnosed of stage III ovarian cancer and 38 (60.3%) of those patients were treated with IP chemotherapy. Of the 38 patients included in the analysis, the median age was 55.5 years and range was 38.6 to 73.8 years. Twenty five patients were treated with upfront debulking surgery followed by adjuvant IP and IV chemotherapy (group 1) and 13 patients were treated with neoadjuvant chemotherapy followed by interim debulking surgery followed by adjuvant IP and IV chemotherapy (group 2). The demographics and clinical characteristics of those patients are included in Table 1. Three patients had stage II disease, and the majority had stage III disease. Two patients had stage IV disease at diagnosis, including one with cytology positive pleural effusion which was drained and did not recur after neoadjuvant chemotherapy, and another patient with a malignant umbilical nodule which was resected during surgery. Three patients were treated with IP therapy after surgery for the first recurrence and they were all in group 1 and received adjuvant treatment. Before starting adjuvant treatment, the baseline CA 125 value was abnormal in 15 (39.5%) patients, more in group 1 (12, 48%) than in group 2 (3, 23%).

### IP treatment characteristics

A modified treatment protocol with Paclitaxel 135 mg/m$^2$ over 3 h on day 1, cisplatin 75 mg/m$^2$ IP on day 2 and paclitaxel 80 mg/m$^2$ IP on day 8 was the standard protocol in this hospital[15]. All patients were treated in the out-patient setting. The first patient who received adjuvant IP and IV treatment in group 1 was in January 2007, and the first patient who received adjuvant IP after neoadjuvant IV treatment was in February 2011.

In group 1, 12 (48%) of the patients completed 4 or more cycle of IP treatment, while the other 52% patients only had 1-3 cycles of IP chemo. In group 2, 8 (61.5%) of the patients completed all 3 cycles of the prescribed IP chemotherapy after surgery, and 2 (15.4%) more patients tolerated more than 3 cycles (Table 2). Twenty three percent of the patients received 1 or 2 IP treatments.

A majority of patients were started the treatment with cisplatin IP at 75 mg/m$^2$ dose, with 96% and 84.6% in group 1 and group 2 respectively. Dose reduction of cisplatin to 60 mg/m$^2$ was seen in 24% in group 1 and 38.5% in group 2. In addition, the dose omission of day 8 IP paclitaxel was common, which occurred in 44% in group 1 and 69.2% in group 2. The delay in starting day 8 treatment due to toxicities was about 20% in both groups. The delay in starting a new cycle of treatment occurred in about 20% of the patients in both groups (Table 2). Three patients did not get IP paclitaxel treatment because they developed allergic reactions to IV paclitaxel, and their treatment was switched to IV albumin-bound paclitaxel on day 1 and 8, without day 8 of IP treatment.

### IV treatment characteristics

The schedule and dosage of IV chemotherapy regimens showed more variations (Table 3). In group 1, those patients who did not complete 6 cycles of IP treatment were more likely to be treated with every 3 wk paclitaxel and carboplatin (14 patients, 56%), and this regimen was used for 7 (54%) patients in group 2 in the neoadjuvant setting. A minority of others used dose dense weekly paclitaxel and carboplatin treatment, or carboplatin backbone in combination with docetaxel, albumin-bound paclitaxel or gemcitabine. A total of 22 (88%) patients in group 1 completed 6 cycles of chemotherapy, including those who received less than 6 cycles of IP containing chemotherapy. Twelve out of 13 (92%) patients in group 2 completed 6 cycles of neoadjuvant IV and adjuvant IV and/or IP treatment.

### Safety profile and side effects

The occurrence of grade 3 or 4 adverse events is summarized in Table 4. Abdominal pain (64% in group 1 and 38.5% in group 2), vomiting (36% in group 1 and 30.8% in group 2), dehydration (16% in group 1 and 15.4% in group 2), and hypomagnesemia (12% in group 1 and 15.4% in group 2) were the most common adverse effects in all patients, while patients who have received neoadjuvant chemotherapy are more likely to get hypokalemia, fatigue and renal insufficiency. Catheter malfunction was only found in 1 patient and there was no treatment related death. Mild hematological toxicities were seen mainly with neutropenia and anemia, and there was no difference in the 2 groups. Prophylactic hydration was scheduled in 28% of the patient in group 1 and 23% of the patients in group 2. Prophylactic hydration was the routine practice with one physician, and was scheduled for every patient on day 4 or 5 and day 11 or 12. Two of the 3 patients who were found to have renal insufficiency were found on the day of planned hydration, and improved after hydration.

**Table 1 Baseline characteristics of the study patients *n* (%)**

| Demographics | Total (*n* = 38) | Adjuvant group (Group 1, *n* = 25) | Neoadjuvant group (Group 2, *n* = 13) |
|---|---|---|---|
| Median age (yr) | 55.5 | 54.3 | 50.1 |
| Range | 38.6-73.8 | 42.1-68.8 | 38.6-73.8 |
| Age groups | | | |
| 30-50 | 16 | 10 | 6 |
| 51-60 | 10 | 8 | 2 |
| 61-75 | 12 | 7 | 5 |
| **Primary site** | | | |
| Ovarian | 37 (97) | 24 (96) | 13 (100) |
| Fallopian tube | 1 (3) | 1 (4) | 0 (0) |
| Tumor stage | | | |
| IIB | 1 (2.6) | 0 (0) | 1 (7.7) |
| IIC | 2 (5.3) | 2 (8) | 0 (0) |
| IIIA | 3 (7.9) | 2 (8) | 1 (7.7) |
| IIIB | 5 (13.2) | 4 (16) | 1 (7.7) |
| IIIC | 22 (57.9) | 14 (56) | 8 (61.5) |
| IV | 2 (5.3) | 0 (0) | 2 (15.4) |
| Recurrent (*n* = 3) | 3 (7.9) | | |
| IIB/C | 2 (8) | 2 (8) | 0 (0) |
| IIIB | 1 (2.6) | 1 (2.6) | 0 (0) |
| Histology | | | |
| High grade serous | 37 (97.3) | 25 (100) | 12 (93.3) |
| Poorly differentiated | 1 (2.7) | 0 (0) | 1 (6.7) |
| Surgery optimal debulking (< 1 cm) | 23 (60.5) | 17 (68) | 6 (46.1) |
| No optimal debulking | 3 (7.9) | 1 (4) | 2 (15.4) |
| Data unavailable | 12 (31.6) | 7 (28) | 5 (38.5) |
| Baseline CA 125 value after surgery[1] | | | |
| Normal | 9 (23.7) | 2 (8) | 7 (53.8) |
| Abnormal | 15 (39.5) | 12 (48) | 3 (23) |
| Not available | 14 (36.8) | 11 (44) | 3 (23) |
| BRCA 1/2 mutations (all germline) | | | |
| Positive | 7 (18.5) | 4 (16) | 3 (23.1) |
| Negative | 16 (42.1) | 12 (48) | 4 (30.8) |
| Unknown | 15 (39.4) | 8 (32) | 7 (53.8) |

[1]Baseline CA 125 value: defined as CA 125 value taken on the day of starting adjuvant treatment, intravenous or intraperitoneal, or in the 2 wk period before chemotherapy.

### *Disease recurrence and OS*

The median follow up of all patients were 48.7 mo (range 4 to 120.3). Ten patients lost to follow up for overall survival (8 in group 1 and 2 in group 2). Four patients lost to follow up for PFS (3 in group 1 and 1 in group 2). For the entire cohort, PFS was 26.5 mo (95% CI 14.9, 38.0). PFS was 26.5 mo (95% CI 14.9, 38.0) in group 1 (adjuvant) and 27.6 mo (95% CI 13.1, 42.1) in group 2 (neoadjuvant) ($P > 0.05$) (Figure 1A and B). The OS was 78.8 mo (95% CI 52.3, 105.4) for the entire cohort, and 100.2 mo (95% CI 67.9, 132.5) for group 1 and 68.2 mo (95% CI 32.2, 104) for group 2 (Figure 1C and D). Three patients were treated with adjuvant IP at the time of first recurrence and the start day for calculation of PFS and OS was the day of second surgery, instead of the initial diagnosis. Nineteen patients received subsequent Bevacizumab treatment when they had further recurrence, 13 (52%) in group 1 and 6 (46%) in group 2 (Table 3).

Seven patients had detectable germline BRCA 1 mutations (Table 5). Five patients were diagnosed at an age older or equal than 50 years old. Three patients demonstrated PFS longer than 50 mo, and 2 of them have not recurred yet. One patient received PARP inhibitor treatment at recurrence.

Five patients (3 in group 1 and 2 in group 2) had no recurrence at the time of censor, the median follow up of these 5 patients were 36.2 mo (range 29.5 to 50.5 mo).

One patient developed a new peritoneal mass which was biopsy proven to be

**Table 2 Treatment characteristics of intraperitoneal chemotherapy *n* (%)**

| Treatment characteristics | Total (*n* = 38) | Adjuvant group (Group 1, *n* = 25) | Neoadjuvant group (Group 2, *n* = 13) |
|---|---|---|---|
| Median | 3 | 3 | 3 |
| Range | (1-6) | (1-6) | (1-4) |
| *Completion of IP cycles* | | | |
| 1 | 5 (13.2) | 4 (16) | 1 (7.7) |
| 2 | 3 (7.9) | 1 (4) | 2 (15.3) |
| 3 | 16 (42.1) | 8 (32) | 8 (61.5) |
| 4 | 9 (23.7) | 8 (32) | 1 (7.7) |
| 5 | 1 (2.6) | 1 (4) | 0 (0) |
| 6 | 4 (10.5) | 3 (12) | 1 (7.7) |
| *IP cisplatin* | | | |
| Starting dose 75 mg/m$^2$ | 35 (92.1) | 24 (96) | 11 (84.6) |
| Dose reduction to 60 mg/m$^2$ | 11 (28.9) | 6 (24) | 5 (38.5) |
| *IP paclitaxel* | | | |
| Dose reduction | 2 (5.3) | 2 (8) | 0/13 (0) |
| Dose omission | 20 (52.6) | 11 (44) | 9 (69.2) |
| Changed to IV abraxane | 3 (7.9) | 1 (4) | 2 (15.4) |
| Treatment delay | | | |
| Delay in starting a new cycle | 8 (21.1) | 5 (20) | 3 (23.1) |
| Delay in day 8 treatment | 8 (21.1) | 5 (20) | 3 (23.1) |
| Prophylactic hydration planned | 10 (26.3) | 7 (18.4) | 3 (21.1) |

IP: Intraperitoneal.

endometroid carcinoma 74 mo after initial surgery while the initial pathology was papillary serous carcinoma. This second diagnosis was treated as a recurrent event in PFS calculation, based on a presumed possibility of an occult mixed histology in the primary occurrence, although a though examination by the pathologist did not show endometroid component.

The 9 mo progression free rate was 88.6% in the entire cohort.

## DISCUSSION

A landmark study (GOG 172) reported median PFS of 23.8 mo and OS of 65.6 mo in patients with advanced ovarian cancer who received IP chemotherapy in the adjuvant setting[4]. However, only 42% patients completed all 6 cycles of IP + IV treatment, and 52% received 4 or more cycles of IP containing therapy in that study. In this retrospective study, we reviewed the outcomes and toxicities of patients who received outpatient IP chemotherapy in a community hospital setting. We found that 48% of the patients tolerated 4 or more cycles of IP chemotherapy after upfront debulking surgery, while 65.5% of the patients could tolerate all 3 cycles of the assigned IP chemotherapy after receiving neoadjuvant IV treatment followed by surgery, and an additional 15.4% patients tolerated 4-6 cycles. Despite a marked variation in the dose and schedule of IV and IP chemotherapy, the entire cohort had a median PFS of 26.5 (95% CI, 15.9, 37.0) mo and OS of 78.8 mo (95% CI 52.3, 105.4). These outcome measures are numerically comparable to those reported in randomized clinical trials[3-5] as well as in the combination analysis[7].

One of the major aims of this study is to study the toxicity profile of IP treatment in patients who have already received 3 cycles of neoadjuvant IV chemotherapy. In this study, we observed abdominal pain (38%-64%), nausea and vomiting (30.8%-36%) and electrolyte abnormalities (4%-30%) to be the most common adverse effects in all patients, while patients who have received neoadjuvant chemotherapy are more likely to get hypokalemia, renal insufficiency and fatigue while receiving IP chemotherapy after surgery. Overall, the magnitude of side effects in this study appeared to be similar to that reported in the GOG 172 study, where the gastrointestinal side effects were 46% and renal side effects were 7%[4]. Importantly, there is no increase in the rate of anemia, neutropenia or thrombocytopenia in the group who have already received neoadjuvant chemotherapy.

**Table 3 Treatment regimen variations in the intraperitoneal therapy, either in the neoadjuvant or adjuvant *n* (%)**

| Treatment regimens | Total, *n* = 38 | Adjuvant group, *n* = 25 | Neoadjuvant group, *n* = 13 |
|---|---|---|---|
| Taxol 175 mg/m$^2$, Carboplatin AUC 5 or 6 every 3 wk | 21 (55.3) | 14 (56) | 7 (54) |
| Carboplatin AUC 5 or 6, Taxol 80 mg/m$^2$ day 1, 8, 15 every 3 wk (dose dense) | 3 (7.9) | 2 (8) | 1 (8)[1] |
| Taxol 80 mg/m$^2$ day 1, 8, Carboplatin AUC 2 day 1, 8 every 3 wk (weekly regimen) | 1 (2.6) | 0 (0) | 1 (8) |
| Carboplatin AUC 5 and Docetaxel 75 mg/m$^2$ every 3 wk | 2 (5.2) | 1 (4) | 1 (8) |
| Carboplatin AUC 5 Gemcitabine 800 mg/m$^2$ day 1, 8 every 3 wk (due to peripheral neuropathy) | 1 (2.6) | 1 (4) | 0 (0) |
| Carboplatin AUC 5 or 6, Abraxane D1, 8 every 3 wk (due to allergic reaction to Taxel) | 3 (7.9) | 1 (4) | 2 (15) |
| Carboplatin AUC with Taxol x1, with Docetaxel x1 and with Gemcitabine x1 (due to allergic reaction) | 1 (2.6) | 1 (4) | 0 (0) |
| No IV treatment, IP treatment only | 6 (15.8) | 5 (20) | 1 (8) |
| Completion of ≥ 6 cycles of IV + IP treatment | 34 (89.5) | 22 (88) | 12 (92) |
| Completion of 7-10 cycles of IV + IP | 5 (13.1) | 2 (8) | 3 (23) |
| Subsequent treatment with Bevacizumab at progression | 19 (50) | 13 (52) | 6 (46) |

[1]This patient also received Bevacizumab with dose dense regimen in the neoadjuvant period. IP: Intraperitoneal; IV: Intravenous.

Catheter problem only occurred in 1 patient in our study, while it was reported to be about 20% and led to treatment discontinuation in the phase III trial[4], which became one of the major concerns of adopting this treatment in the community. We did not encounter infection or catheter occlusion; and other than proper training our nursing staff received, there was no particular extra care to the IP catheters.

Prophyalctic hydration was a routine practice with one physician and 2 cases of renal insufficiency were found on day 4 or 5 which were planned hydration days. In those patients who did not have planned hydrations, this transient change of renal function could be missed thus underdiagnosed.

Comparing to the most relevant bench marker study, which is the randomized phase II/III OV21/PETROC study presented in American Society of Clinical Oncology 2016[13], the rate of adverse effects in our cohort is much higher. In the above 3 arm study, patients received neoadjuvant chemotherapy followed by surgery and were then randomized to receive IV Paclitaxel day 1, day 8 and carboplatin IV day 1 (arm 1), or the same IV-IP protocol we followed in our cohort, which is cisplatin IP day 1, paclitaxel IV day 1 and paclitaxel IP day 8 (arm 2). The patients in arm 3 received carboplatin AUC 5 or 6 IP substituting cisplatin IP on day 1 with the rest same as in arm 2. The IP cisplatin containing arm (arm 2) was considered to be inferior and was discontinued. In their report, side effects equal or more than grade 3 occurred in only less than 10% of the patients, which is much less than in our patients. One of the reasons for this difference could be due to the elimination of IP cisplatin in early stage of the OV21/PETROC trial. In terms of outcome measure, the progression rate at 9 mo was 42% in arm 1, and 24.5% in arm 3 showing favorable result in the IP arm. In our study, the 9 mo progression free rate of the entire cohort was 88.6%. Due to the small sample size in our study, this large difference may not be statistically significant. However, it did show an excellent treatment response produced in our patients.

Overall, our analysis showed that administrating IP chemotherapy after neoadjuvant chemotherapy and surgery is doable. Although it appeared to be associated with more GI and renal side effects, about half of the patients can endure all three cycles.

Incorporating IP treatment in the adjuvant treatment of stage III and IV ovarian cancer patients in our institution, whether or not they have received neoadjuvant chemotherapy, was inspired by the large difference in PFS (23.8 mo *vs* 18.3 mo) and

**Table 4 Safety profile and side effects (grade 3 or 4) *n* (%)**

| Toxicities | Adjuvant group, *n* = 25 (100) | Neoadjuvant group, *n* = 13 (100) |
|---|---|---|
| Abdominal pain/pelvic pain | 16 (64) | 5 (38.5) |
| Nausea/vomiting | 9 (36) | 4 (30.8) |
| Fatigue | 2 (8) | 2 (15.4) |
| Renal insufficiency | 0 (0) | 3 (23.1) |
| Dehydration/hypotension | 4 (16) | 2 (15.4) |
| Catheter malfunction/infection | 1 (4) | 0 (0) |
| Anemia | 3 (12) | 1 (7.7) |
| Thrombocytopenia | 1 (4) | 0 (0) |
| Neutropenia | 5 (20) | 1 (7.7) |
| Hypokalemia | 1 (4) | 4 (30.8) |
| Hypomagnesemia | 3 (12) | 2 (15.4) |

OS (65.6 mo *vs* 49.7 mo) demonstrated in the GOG 172 study[4] and supported by others[3,5]. This approach has been challenged, and it is now a subject of debate regarding the definitive benefit with IP therapy in the era of applying inhibition of vascular endothelial growth factor (VEGF) pathway. Adding VEGF targeting agent Bevacizumab to the chemotherapy backbone and extending its use for a prolonged period has been evaluated in GOG 218[9] and ICON-7 study[10], and both studies showed improvement in PFS and OS in high risk patients. In June 2018, Genentech[16] reported an updated analysis of GOG 218 showing improvement in PFS from 12 mo to 18.2 mo and a hazard ratio of 0.62 by adding Bevacizumab to chemotherapy. Bevacizumab has received approval by Food and Drug Administration for upfront adjuvant treatment in stage III or IV ovarian cancer after initial debulking surgery[16].

Delivery of chemotherapy in a dose dense (weekly) fashion may offer therapeutic advantage, as shown in the Japanese study (median PFS of 28 mo), longer than the conventional every 3 wk chemotherapy (median PFS 17.2 mo)[17]. Data from the GOG 252 study showed a less impressive difference with dose dense treatment chemotherapy (14.2 mo *vs* 10.3 mo) only among those patients who did not receive bevacizumab as part of the adjuvant treatment[11]. A more direct comparison was carried out by the NRG/GOG 256 and was presented in 2016 SGO meeting[18]. This study randomized patients to IV dose dense chemotherapy, IP carboplatin with IV weekly paclitaxel, and IP cisplatin, IP paclitaxel and IV paclitaxel, and bevacizumab was added in all 3 arms[18]. There was no difference in PFS among the three arms, albeit the PFS was much better in all the arms than that in the previous studies. As all patients received treatment with IV bevacizumab, it is possible that the additional therapeutic effect of bevacizumab has overshadowed the benefit gained from IP therapy. In addition, the dose of IP cisplatin was 100 mg/m$^2$ in the original GOG 172 study, while it was 75 mg/m$^2$ in the NRG study, suggesting the importance of the treatment effect with high dose cisplatin. Adding to the controversy of the benefit of IP chemotherapy is the new report from the phase III study applying hyperthermic IP chemotherapy with cisplatin 100 mg/m$^2$ or not during interim surgery in patients already received neoadjuvant IV chemotherapy[19]. The addition of hyperthermic IP versus surgery alone leads to improvement in both PFS and OS with HR of 0.6. The median recurrence free survival was 10.7 mo in the surgery group and 14.2 mo in the surgery plus hyperthermia group. The median OS was 33.9 mo in the surgery group and 45.7 mo in the surgery plus hyperthermia group. The result supports the intraperitoneal approach of treatment. Whether the therapeutic effect is a result of hyperthermia or the high effective dose of cisplatin IP at 100 mg/m$^2$ is still unclear, and further confirmatory trials are needed[20].

Our observation of median PFS of 26.5 mo and OS of 78.8 mo in the entire cohort of 38 patients who received IP chemotherapy is significant. Despite the variations in dose, schedule, and chemotherapy agent choice, these measures are numerically longer than reported studies in the literature, such as the EORTC neoadjuvant study[12], the IV therapy only arms in GOG 172[4], and the arm with Bevacizumab in the GOG 218 study[9]. Our observation should add useful information to the medical literature regarding the clinical experience and benefit of incorporating IP chemotherapy in ovarian cancer treatment in the community setting.

The limitation of the study is its retrospective nature and its small sample size. There was sometimes limitation and deficiencies in the documentation of adverse events particularly in patients in group 1. When a patient was not scheduled to come

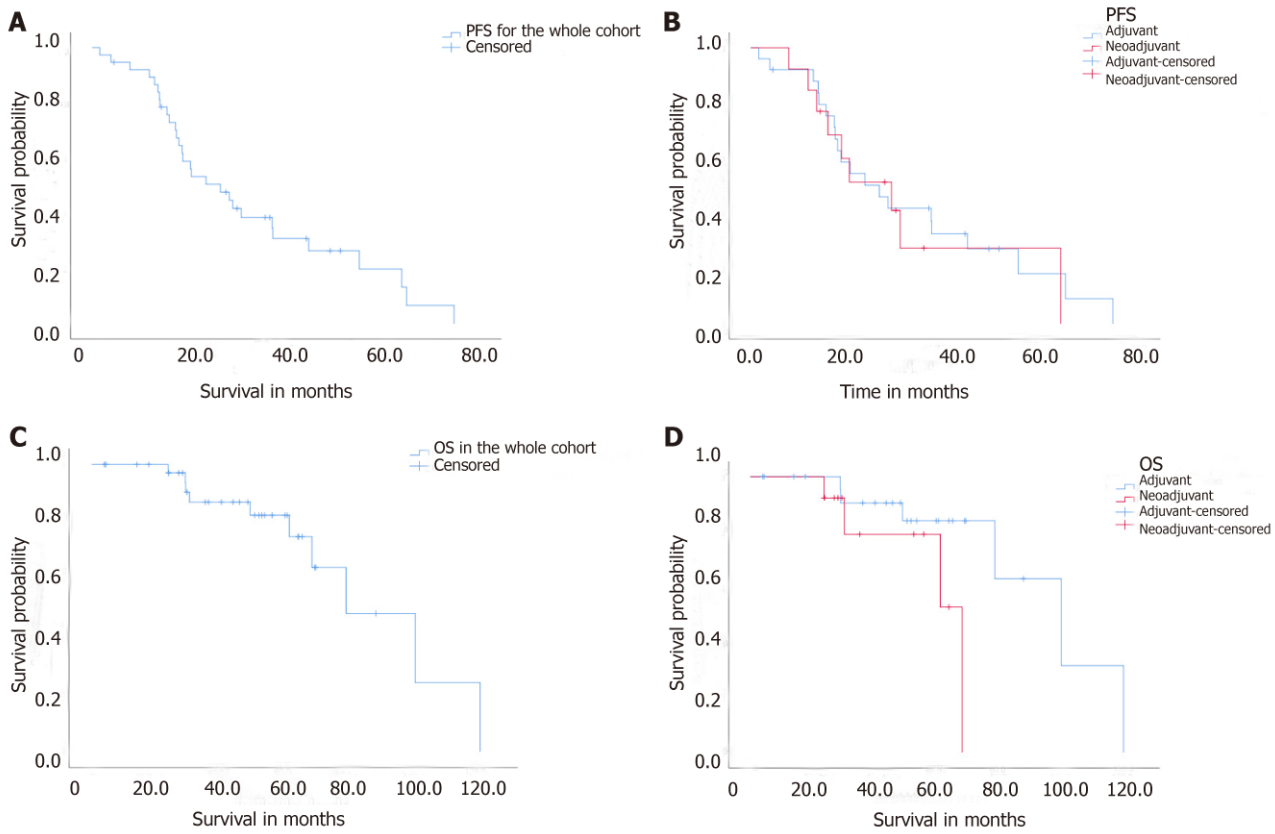


**Figure 1 Kaplan-Meier survival curves survival among ovarian cancer patients.** A: Progression free survival (PFS) in the whole cohort; B: PFS in the adjuvant and neoadjuvant groups; C: Overall survival (OS) in the whole cohort; D: OS in the adjuvant and neoadjuvant groups. PFS: Progression free survival; OS: Overall survival.

back to the clinic for an interim lab test, a nadir in the counts of white blood cell, hemoglobin or platelet counts may be missed. The pattern of management among physicians varied among treatment physicians, and routine schedules of hydrations on day 4 and day 10 were applied by one physician which possibly lead to better capture of adverse events. Our data set is also extremely small in the evaluation of PFS or OS.

In conclusion, our findings suggest that the administration of IP chemotherapy is feasible in both settings of after upfront surgery and after neoadjuvant IV therapy followed by interim surgery. It can be safely administrated in the community cancer clinic setting. The use of IP/IV chemotherapy in patients who have received neoadjuvant chemotherapy is tolerable. Despite various schedule modifications, dose reductions and shortening of treatment courses, incorporation of IP chemotherapy in the adjuvant treatment of ovarian cancer appears to improve disease free survival and OS.

**Table 5 The characteristics of patients with BRCA germline mutations**

| Serial Number | Age at diagnosis (yr) | BRCA mutation | Significance | Group assignment | PFS per study (mo) | PFS[1] | Recurrence |
|---|---|---|---|---|---|---|---|
| 3 | 50 | BRCA 1, Q1395X (4302C>T) | Deleterious | 1 | 51.2+ | 73.2+ | No |
| 4 | 52 | BRCA 1, 187del AG | Deleterious | 1 | 15.5 | | Yes |
| 7 | 58 | BRCA 1, Q310X | Deleterious | 1 | 14+ | 36+ | No |
| 22 | 56 | BRCA 1, G1706E | Suspected deleterious | 1 | 23.5 | | Yes, deceased |
| 23 | 54 | BRCA 1, unknown | Deleterious | 1 | 12.9 | | Yes |
| 28 | 41 | BRCA 1, C64G (309T>G) | Deleterious | 2 | 35.7+ | 53 | Splenic recurrence, at 53 mo |
| 35 | 40 | BRCA 1, 187delAG | Deleterious | 2 | 29.9+ | 51.9+ | No |

[1]Progression free survival (PFS) used the cut of day of 1/30/2019. PFS per study used cut off day of March 30, 2017. PFS: Progression free survival.

## ARTICLE HIGHLIGHTS

### *Research background*

Adjuvant chemotherapy using intraperitoneal (IP) treatment has demonstrated survival benefit over intravenous (IV) therapy alone in patients treated with upfront debulking surgery for advanced stage ovarian cancer based on the Gynecologic Oncology Group (GOG) 172 trial. Neoadjuvant chemotherapy followed by interim surgery and adjuvant chemotherapy has similar outcome in survival as compared to upfront surgery followed by adjuvant IV chemotherapy based on the European Organization for Research on Treatment of Cancer study. IP chemotherapy has not been widely adopted in clinical practice for a number of reasons, mainly due to the concern of side effects. With the wide spread use of neoadjuvant chemotherapy, it is unclear whether IP chemotherapy in the adjuvant setting in those patients is safe and beneficial. There is an ongoing phase III study (OV21/PETROC) addressing this questions, and its preliminary result showed increase in progression free survival (PFS) in the IP arm compared to IV arm (42% *vs* 24.5%) using 9 mo progression rate as the outcome measure.

### *Research motivation*

There are multiple problems to be addressed regarding IP chemotherapy. (1) What are the side effects of IP treatments, especially off clinical trials in a community cancer center? (2) Would patients experience more side effects after they have received neoadjuvant IV chemotherapy and then receive IP chemotherapy in the adjuvant setting? And (3) Is there benefit or improved outcome in those patients who receive IP chemotherapy? As our cancer center recommended IP chemotherapy to all fit patients as a general practice, we decided to analyze our data to answer those questions. We hope to share our community experience and to show the safety and efficacy data, to decrease the concerns regarding the side effects of IP, and to support the use of IP in the right clinical setting.

### *Research objectives*

We wished to evaluate the experience of adjuvant IP chemotherapy in the community cancer clinic setting, and the clinical benefit and tolerability of incorporating IP chemotherapy in patients who have received neoadjuvant treatment.

### *Research methods*

We retrospectively evaluated toxicities and outcomes of patients with stage III and IV ovarian cancer diagnosed at our institution between 07/2007 and 07/2015 who received intraperitoneal chemotherapy after cytoreductive surgery (group 1) or after neoadjuvant chemotherapy followed by interim surgery (group 2). We reviewed the electronic records, and documented the regimens used, dose reduction, dose delay, drug variations. We also documented toxicities, patient characteristics.

We performed a sample size calculation to determine the least number of patients to be included in the study to have an 80% power to compare with the historical data (60 mo for the IP group reported in the GOG 172 study), and came up with 31 patients. We actually had 38 patients, which should have the above power to have a comparison.

We specified that PFS will be calculated starting from the date of diagnosis to the date of progression on computed tomography scan or death or last known follow up. Three patients were treated at the first recurrence with IP after surgery, and we defined the diagnosis date to be the date of the second debulking surgery, which was used as the start date for PFS and overall survival (OS) calculations. For some patients who lost for follow up and had Medicare insurance,

we checked Medicare data base to extract date of death.

### Research results

Thirty eight patients were treated with IP chemotherapy, median age was 54 years old (range 38.6 to 71 years). In group 1 ($n$ = 25), 12 (48%) of the patients completed 4 or more cycle of IP treatment after upfront debulking surgery; while in group 2 ($n$ = 13), 8 (61.5%) of the patients completed all 3 cycles of the assigned IP chemotherapy after receiving neoadjuvant IV chemotherapy followed by surgery, and 2 (15.4%) more patients tolerated more than 3 cycles. In those patients who did not get planned IP chemotherapy, most of them were treated with substitutional IV chemotherapy, and the completion rate for 6 cycles of IV + IP was 92%.

Abdominal pain, (64% in group 1 and 38% in group 2), vomiting (36% in group 1 and 30.8% in group 2), dehydration (16% in group 1 and 15.4% in group 2), and hypomagnesemia (12% in group 1 and 15.4% in group 2) were the most common adverse effects in all patients, while patients who have received neoadjuvant chemotherapy were more likely to get hypokalemia, fatigue and renal insufficiency.

PFS was 26.5 mo (95% CI 14.9, 38.0) in group 1 and 27.6 mo (95% CI 13.1, 42.1) in group 2. OS was 100.2 mo (95% CI 67.9, 132.5) for group 1 and 68.2 mo (95% CI 32.2, 104.0) for group 2. For the entire cohort, PFS was 26.5 mo (95% CI 15.9, 37.0) and OS was 78.8 mo (95% CI 52.3, 105.4). The 9-mo PFS rate was 88.6% in the entire cohort.

Our result reflected the real world experience of IP administration, in that most of the patients did not get 6 cycles of IP for adjuvant treatment as in GOG 172 study. About half of the patients can get 3 cycles of IP treatment, which was also true in those patients who have received neoadjuvant treatment. There appears to be benefits in PFS and OS even with the above limitations.

### Research conclusions

The use of IP/IV chemotherapy can be safely administrated in the community cancer clinic setting. The use of IP/IV chemotherapy in patients who have received neoadjuvant chemotherapy followed by surgery is feasible and tolerable. Despite various modification of the IP regimen, incorporation of IP chemotherapy in the adjuvant setting appears to be associated with improved progression free survival and overall survival.

Our data provides community practice experience and supports the data reported in GOG 172 and Cochran review from clinical trials about the benefits and toxicities of IP therapy. The benefit of IP treatment remains sizable even with reduced cycles of IP and dose variations.

Our study provides new information on the benefits and toxicities of administration of adjuvant IP in patients who have received neoadjuvant IV chemotherapy. A phase III OV21/PETROC study has been designed to address this question, and our 9-mo PFS rate was higher than reported in the study.

### Research perspectives

In our community practices, administration of IP chemotherapy in the adjuvant treatment for ovarian cancer, and in patients who have received IV chemotherapy in the neoadjuvant setting, is feasible, safe and associated with apparent benefit in PFS and OS. This approach should be further studied in randomized phase III clinical trials.

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CASE REPORT

# Clear cell sarcoma in unusual sites mimicking metastatic melanoma

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## Abstract

*BACKGROUND*

Clear cell sarcoma is an aggressive rare malignant neoplasm with morphologic and immunohistochemical similarities to malignant melanoma. Both disease entities display melanin pigment and melanocytic markers, making differentiation between the two difficult. Although clear cell sarcoma cases in the literature have mainly involved deep soft tissues of the extremities, trunk or limb girdles, we report here two cases of primary clear cell sarcoma in unusual sites and describe their clinicopathologic findings.

*CASE SUMMARY*

The first case involves a 37-year-old female, who presented with jaw pain and a submandibular mass. The second case involves a 33-year-old male, who presented with back pain and a thoracic spine tumor. Both cases showed tumors with diffuse infiltration of neoplastic cells that were positive for melanocytic markers, and in both cases this finding led to an initial diagnosis of metastatic melanoma. However, further analysis by fluorescence *in situ* hybridization (commonly known as FISH) showed a rearrangement of the EWS RNA binding protein 1 (*EWSR1*) gene on chromosome 22q12 in both patients, confirming the diagnosis of clear cell sarcoma.

*CONCLUSION*

Distinction between clear cell sarcoma and malignant melanoma can be made by FISH, particularly in cases of unusual tumor sites.

**Key words:** Clear cell sarcoma; Melanoma; Salivary gland; Spine; Fluorescence in situ hybridization; Case report



**Core tip:** The diagnosis and management of clear cell sarcoma can be a clinical dilemma. Recognition of the clinicopathologic pattern and differentiating it from malignant

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melanoma can prevent misdiagnosis. This case report not only represents the first reported occurrence of clear cell sarcoma in the submandibular gland in the literature but also identifies another unusual location of involvement, the thoracic spine. It is important to promptly recognize this disease entity because early treatment is necessary to prevent fatal consequences.

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## INTRODUCTION

Clear cell sarcoma (also known as melanoma of the soft parts) was initially described by Dr. Franz Enzinger[1] in 1965, when he identified it as a sarcoma arising from the tendons and aponeurosis of extremities with a distinctive clinical and morphological pattern. Today, we understand clear cell sarcoma to be an aggressive tumor that accounts for only 1% of all soft tissue sarcomas, affecting mainly adolescents and young adults, and associated with local recurrences and late metastasis. Although both malignant melanoma and clear cell sarcoma display similar melanocytic markers, the two disorders are genetically distinct. Cases of malignant melanoma may contain *BRAF* mutations[2], whereas clear cell sarcoma lacks this mutation[3] and characteristically exhibits the reciprocal translocation t(12;22)(q13;q12) resulting in a rearrangement of the EWS RNA binding protein 1 (*EWSR1)* gene[4,5].

Clear cell sarcoma of the head and neck are uncommon[6,7]. Tumors arising from the salivary glands are extremely rare but have been described previously in the parotid gland[8-10]. Similarly, clear cell sarcoma of the thoracic spine or paraspinal soft tissues is very rare and very few cases have been reported[11]. To our knowledge, no cases of clear cell sarcoma of the submandibular gland have been published in the literature. We report herein the clinicopathologic findings of two cases of primary clear cell sarcoma arising in the submandibular gland and the thoracic spine, respectively, and highlight the challenges in their diagnosis as well as the importance of molecular genetics in differentiating this tumor type from malignant melanoma.

## CASE PRESENTATION

### *Case 1*

**Chief complaints:** A 37-year-old female presented to our hospital with complaint of left jaw pain and swelling.

**History of present illness:** The patient reported the symptoms having been present for 6 mo.

**History of past illness:** The patient's past medical history was unremarkable.

**Physical examination:** A left neck mass was felt on palpation.

**Laboratory testing:** Histological assessment of a fine-needle aspirate of the mass showed epithelioid-looking neoplastic cells with enlarged eccentric nuclei and prominent nucleoli. Based on these cytomorphologic features, the differential diagnosis of a high-grade carcinoma, hyalinizing clear cell carcinoma, and malignant melanoma was proposed.

**Surgical investigation and resection:** The patient was referred to the surgical team and based on the preliminary diagnosis, it was decided that the mass should be resected along with regional lymph node dissection. The patient underwent a left neck dissection and excision of the left neck mass. Histopathologic examination revealed nests of poorly differentiated malignant cells with pleomorphic vesicular nuclei, mitotic figures and clear cytoplasm (Figure 1). The tumor cells had invaded the adjacent soft tissue but no bone involvement was present. The cervical lymph node dissection yielded two metastatic adenopathies among the eighteen dissected lymph nodes. Immunohistochemical staining showed that the neoplastic cells were positive

for Human Melanoma Black-45 (commonly known as HMB-45; a melanocytic tumor marker) (Figure 2A), S-100 (Figure 2B) and vimentin, but were negative for cytokeratin (Figure 2C), calponin, smooth muscle actin, synaptophysin, chromogranin, and glial fibrillary acidic protein. Some of the tumor cells contained melanin pigment, which reacted positively in Masson Fontana staining (Figure 2D). These results supported the initial diagnosis of malignant melanoma and excluded the diagnosis of a clear cell carcinoma due to negativity for cytokeratin.

### Case 2

**Chief complaints:** A 33-year-old male presented to our institution with complaint of mid back pain radiating to the flanks, and leg weakness and numbness, with gait abnormalities.

**History of present illness:** The patient reported the symptoms having been present for 6 mo.

**History of past illness:** The patient had no past medical history.

**Physical examination:** On physical examination, the patient showed a wide-based, unsteady gait, with weakness and decreased sensation and reflexes in both lower limbs.

**Imaging examination:** An MRI scan showed a mass enhancement in the T6 and T7 region of the spine (Figure 3A), raising suspicion of a paraspinal mass causing compression on the spinal cord.

**Surgical investigation and resection:**The patient was referred to the neurosurgical team, who decided to completely resect the tumor for pathological assessment to determine the diagnosis. A T6-7 laminectomy was performed, with complete resection of the tumor. Intraoperatively, the tumor was found to grossly involve the thoracic spine, with predominant involvement of the paraspinal soft tissues. Pathological examination of the resected neoplasm showed fascicles and nests of spindle cells (Figure 3B) with epithelioid features, eosinophilic cytoplasm, occasional mitosis, and pigment in some of the cells (Figure 3C). The tumor cells were positive for HMB-45 (Figure 3D), S-100 and melanoma antigen (Melan-A), but were negative for cytokeratin, desmin, smooth muscle actin, and glial fibrillary acidic protein. The pigment in the tumor cells was confirmed to contain melanin by reacting positivity with the Masson Fontana stain. These results supported the initial diagnosis of malignant melanoma.

## MULTIDISCIPLINARY EXPERT CONSULTATION

### Case 1

The case was sent out to two different institutions, with all subsequent experts agreeing with the diagnosis of melanoma. An extensive dermatological, ophthalmological and radiological workup of the patient was performed to rule out a primary site. Skin and mucosal surfaces did not reveal any suspicious lesions. A whole-body positron emission tomography/computed tomography scan and magnetic resonance imaging (MRI) of the head and neck region did not show any ocular involvement or masses in any other sites.

### Case 2

This case was handled fully within our institution by the clinical staffs described.

## FINAL DIAGNOSIS

### Case 1

At this time, the diagnosis was melanoma.

### Case 2

Because our past experience had taught us that clear cell sarcoma can readily mimic malignant melanoma, a FISH study was ordered. An *EWSR1* gene rearrangement on chromosome 22q12 was found (Figure 4). This confirmed the diagnosis of clear cell sarcoma of the thoracic spine involving the paraspinal soft tissues.

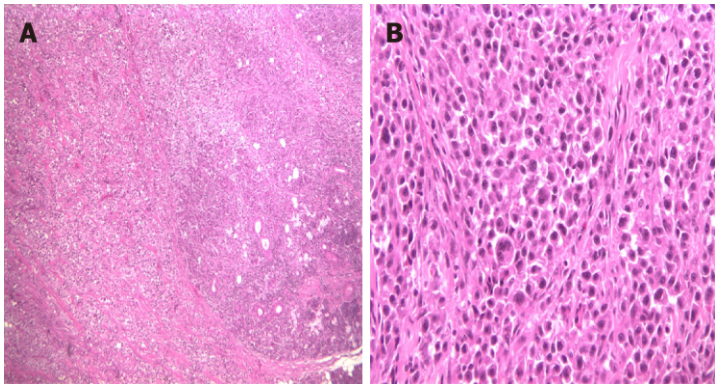


**Figure 1 Histopathology of the submandibular gland mass in Case 1.** A: Section of the mass showed nests of poorly differentiated tumor cells infiltrating into the benign acinic cells (HE,× 50); B: Neoplastic cells displayed pleomorphic, bizarre nuclei with prominent nucleoli and mitotic figures (HE,× 400). HE: Hematoxylin and eosin.

## TREATMENT

### *Case 1*

The patient was started on adjuvant therapy with interferon alpha-2 (18 MIU three times a week for 8 wk). Two months later, the patient developed an enlarged left supraclavicular lymph node. She was started on localized radiation (4 fractions of 8 Gy weekly) to the supraclavicular node, in addition to the interferon 2-alpha she was currently on. While on treatment, the tumor progressed to involve the left pterygoid region, extending towards the inferior aspect of the left masseter muscle and the temporalis muscle. The patient underwent an extensive resection of the tumor with partial removal of her left jaw, followed by additional radiation therapy.

## OUTCOME AND FOLLOW-UP

### *Case 1*

Four months later, the patient presented with metastatic disease to the lungs, spine and left neck soft tissue, and died shortly afterward. On further review at 8 years later, we sent the resected tumor specimen for retrospective florescence *in situ* hybridization (FISH). A rearrangement of the *EWSR1* gene on chromosome 22q12 was found, confirming the diagnosis of clear cell sarcoma.

### *Case 2*

Following surgery, a repeat MRI showed no evidence of residual tumor. Apart from lower back pain which was managed with pain medications, the post-operative course was uncomplicated. The patient was able to slowly ambulate with mild muscle weakness. The patient was discharged and referred to physical therapy for rehabilitation. Two months post-surgery, the patient was stable, ambulatory and undergoing physical therapy with no recurrence of the thoracic tumor on MRI. Adjuvant standard fractionation radiotherapy (2 Gy a day) was given for 5 d. At 6 mo post-surgery follow-up visit, MRI showed post-surgical changes in the mid thoracic region with no evidence of a recurrent tumor. Currently the patient has intermittent lower back pain due to poor posture and has no neurological deficits. His muscle strength has greatly improved due to compliance with physical therapy. The patient will be monitored closely for recurrence with MRI every 6 mo.

## DISCUSSION

Clear cell sarcoma typically involves tendons and aponeurosis[1,12] of adolescents and young adults of both sexes. The tumor usually presents as a small insidiously growing mass, but it can suddenly become aggressive and rapidly metastasize, as was observed in our patient (Case 1). Following Enzinger's initial description of the clear cell sarcoma, Chung and Enzinger[12] demonstrated melanin in 72% of tumors with clear cell sarcoma, supporting their origin from migrated neural crest cells. As such, they coined the name "malignant melanoma of soft parts", which seems preferable over the more descriptive term of clear cell sarcoma. In addition, clear cell sarcoma

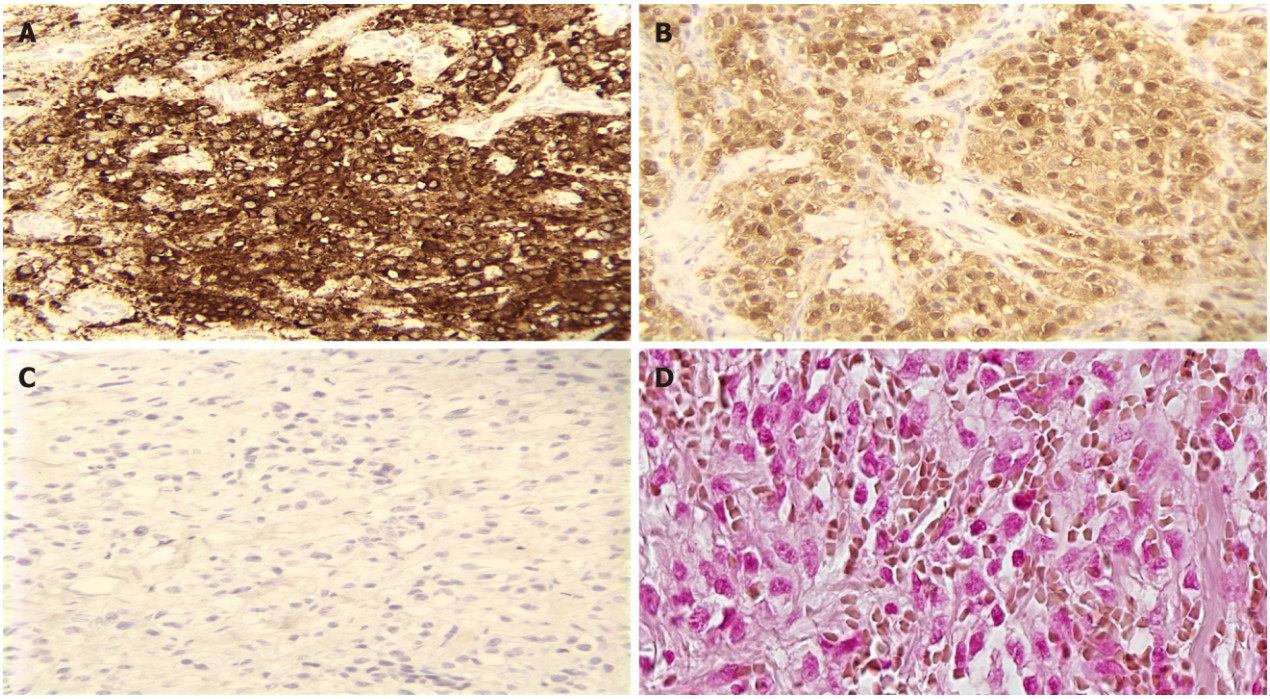


**Figure 2 Immunohistochemistry of the submandibular mass in Case 1.** A-C: The tumor cells demonstrated positive staining for (A) Human Melanoma Black-45 (× 400) and (B) S-100 (× 400) and negative staining in neoplastic cells for (C) keratin (× 400); D: The melanin pigment in the tumor cells showed positive reaction to Masson Fontana stain (× 400).

has been shown to be positive for antigens associated with the synthesis of melanin, such as HMB-45, S-100 protein and Melan-A[13,14]. Moreover, electron microscopy has demonstrated melanosomes in clear cell sarcoma, similar to malignant melanoma. For these reasons, clear cell sarcoma is thought to be a subtype of malignant melanoma, albeit genetically distinct. Typically, cases of clear cell sarcoma have a reciprocal translocation [t(12;22)(q13;q12)] resulting in an *EWSR1*-activating transcription factor (*ATF)* gene fusion[4,5,15]. The second major differential diagnosis of clear cell sarcoma will include a clear cell carcinoma, such as the hyalinizing clear cell carcinoma; however, carcinomas are readily diagnosed by immunohistochemistry, which should show a positive cytokeratin stain.

Herein, we present first a case of clear cell sarcoma occurring in the submandibular gland (Table 1) that closely resembled a malignant melanoma on histological analysis. There was a concurrence of the initial malignant melanoma diagnosis when two outside institutions were consulted. The initial misdiagnosis was due to the morphologic and immunohistochemical similarities between clear cell sarcoma and malignant melanoma and lack of awareness of the t(12;22)(q13;q12) translocation, which was only recently described. Immunohistochemistry excluded a clear cell carcinoma, smooth muscle tumors, neuroendocrine neoplasms, or primary brain tumors. Additional supportive findings for the case to be a primary clear cell sarcoma are that the lesion was solitary and metastasis was present only in the cervical lymph nodes draining from the submandibular mass. These findings illustrate the typical spread of clear cell sarcoma from a primary site to regional lymph nodes[12,14]. Secondly, there was absence of malignancy elsewhere in the body, thereby supporting our diagnosis of a primary clear cell sarcoma arising from the submandibular gland. To our knowledge, this is the first report to describe a case of primary clear cell sarcoma of the submandibular gland. In general, clear cell sarcoma of the salivary gland is extremely rare. At the time of this report only three cases involving the salivary gland have been published, all of which had arisen in the parotid gland and were treated surgically[8,10]. Only one of those cases[10] recurred after surgery, and the patient was alive with no evidence of the disease after radical neck surgery and adjuvant radiotherapy.

Our second case presented with a T6-7 paraspinal mass, which was given an initial diagnosis of malignant melanoma. Based on our previous experience we performed FISH testing, which demonstrated the *EWRS1* rearrangement and confirmed the diagnosis of clear cell sarcoma. Clear cell sarcoma of the thoracic spine or paraspinal soft tissues is extremely rare. Gao *et al*[11] found only four cases reported in the literature. All of these presented with back pain. Two of these patients were treated

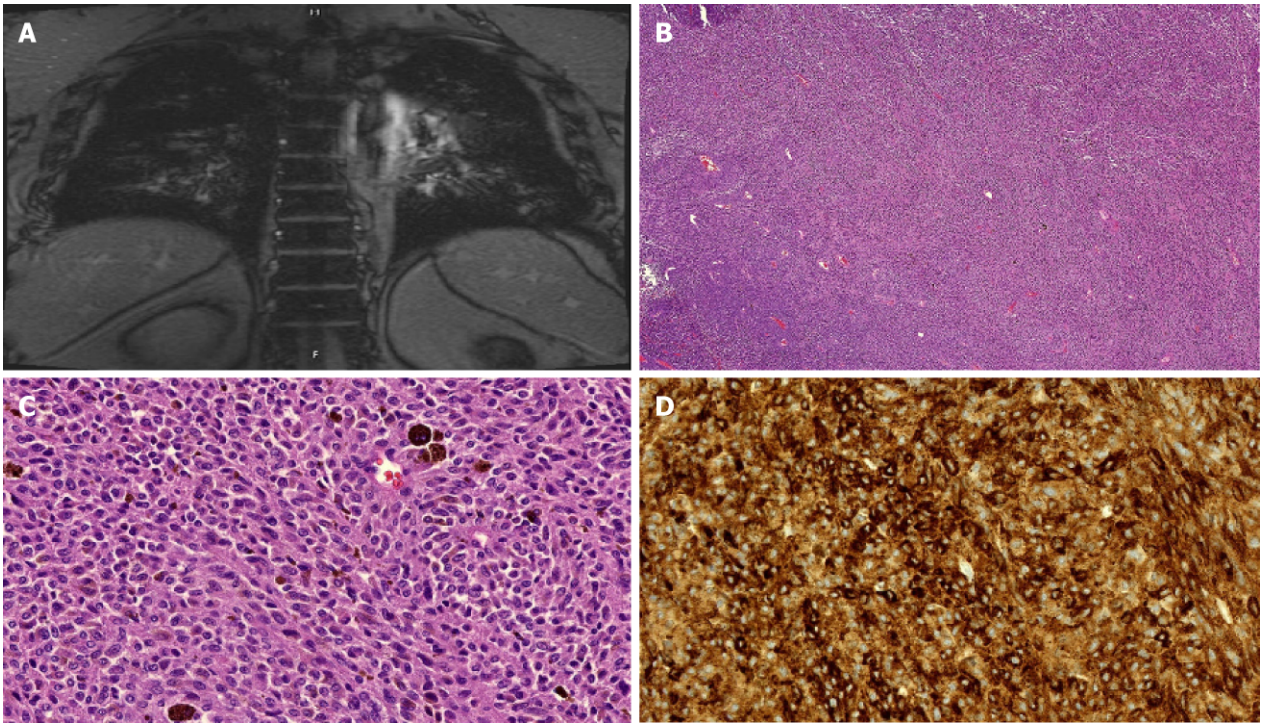


**Figure 3 Radiology and pathology of the thoracic paraspinal mass in Case 2.** A: Magnetic resonance imaging of the tumor showed an enhancing thoracic spine mass involving the paraspinal soft tissues; B: Sections of the mass showed fascicles and nests of spindle cells (HE, × 50); C, D: Neoplastic cells displayed melanin pigments (HE, × 400) and positivity for Human Melanoma Black-45 by immunohistochemistry (× 400). HE: Hematoxylin and eosin.

successfully by complete resection of the tumor with clear margins, while another patient was treated with surgery and chemotherapy, and experienced local recurrence[16]. There was no follow-up information for the fourth case[17]. Surgery is the mainstay of treatment for clear cell sarcoma, with chemotherapy having little effect[18,19]. About a third of patients with clear cell sarcoma receive radiotherapy mostly in conjunction with surgery. Although radiation therapy has been shown to reduce the size of these tumors, clear beneficial effects of radiotherapy alone is difficult to assess since most cases are given either pre- or post-operatively[18,19]. Chemotherapy is predominantly used in patients with metastatic disease, however, prognosis is very poor, with an estimated 5-year survival rate of only 15%[18,20]. Targeted therapies, such as receptor tyrosine kinase inhibitors and histone deacetylase inhibitors, have shown benefit in some patients with this high-grade sarcoma, but most of these treatment strategies have so far only been applied in clinical trial settings[21]. Although surgery remains the treatment of choice for clear cell sarcoma, these tumors tend to recur. The reported rates of local recurrence of clear cell sarcoma following surgery reach up to 84%, with late metastases up to 63% and metastases at presentation up to 30%[5,14]. A recent review by Gonzaga *et al*[22] showed that the approximate 5- and 10-year overall survival for 489 patients with clear cell sarcoma was 50% and 38%, respectively. The estimated 5-year survival for Stages I–IV was 75%, 65%, 35% and 15%, respectively. In addition, the mean survival for Stage I was 94.9 mo, Stage II was 94.7 mo, Stage III was a median of 24.9 mo, and Stage IV was a median of 8.9 mo. Our first patient (case1) underwent complete excision of the tumor but the patient had metastasis to the regional lymph nodes. It is possible that the metastatic lymph nodes were not completely excised which led to recurrence. Although the diagnosis of the patient was not evident at the time, the patient received the correct modalities of therapy published in the literature which included surgery and radiotherapy. However, the aggressiveness and rapid progression of the disease led to fatal consequences. The second patient had complete surgical resection with adjuvant radiation treatment. The patient is currently stable with an estimated 5-year survival of about 70% based on prior studies[22]. We recently reported a case of clear cell sarcoma of the dermis that was completely excised and the patient is currently disease free two years post resection[23]. Based on our limited experience and published literature, it appears that early detection and tumor resection is the key to good clinical outcome[22,23]. Due to the rarity of the entity in the submandibular gland and thoracic spine, it is not possible at present to predict the outcome of treatment in the afflicted patients.

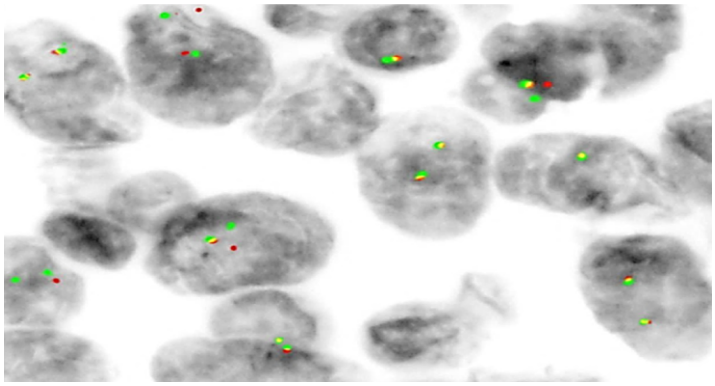

**Figure 4 Fluorescence *in situ* hybridization analysis of the spinal tumor in Case 2.** Fluorescence *in situ* hybridization using a dual-color, break-apart probe for EWSR1 demonstrated one normal fusion (yellow) along with an extra red signal and extra green signal, indicating translocation.

## CONCLUSION

Clear cell sarcoma of the submandibular gland and thoracic spine or paraspinal soft tissues are rare disease entities. The presentation, histology, and tumor prognosis appear to be similar to the clear cell sarcoma arising elsewhere. FISH studies should be done on all tumors that demonstrate melanocytic markers without a cutaneous or mucosal malignant melanoma, to prevent a misdiagnosis of malignant melanoma. Although malignant melanoma and clear cell sarcoma are both aggressive tumors, it is important to differentiate between the two because of their different underlying pathophysiological pathways and therapeutic implications.

**Table 1 Timeline of patient history and medical intervention of case 1**

| Dates | Relevant past medical history and intervention | | |
|---|---|---|---|
| | Summaries from initial and follow-up visits | Diagnostic testing | Interventions |
| July 2009 | Patient presented with a 6-mo history of left jaw pain and mass | Cytological examination of fine-needle aspirate of the mass | Surgical resection of the neck mass |
| July 2009 | Post-surgery follow-up | A whole-body PET/CT scan and MRI of the head and neck region | Interferon alpha-2 (18 MIU three times a week for 8 wk) |
| September 2009 | On routine follow-up, an enlarged left supraclavicular lymph node was identified | PET/CT scan | Radiotherapy to the supraclavicular node in addition to the interferon alpha-2 |
| October 2009 | Metastatic disease to the left pterygoid region, masseter muscle and the temporalis muscle | PET/CT scan and MRI | Complete resection of involved areas with adjuvant weekly radiotherapy |
| February 2010 | Metastatic disease to the lungs, spine and left neck soft tissue | PET/CT scan and MRI | Expired within a wk |

MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography.

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