Surgery with hyperthermic intraperitoneal chemotherapy after response to induction chemotherapy in patients with peritoneal metastasis of gastric cancer

Emel Canbay1, Bahar Canbay Torun2, Kaan Cosarcan3, Cetin Altunal1, Bulent Gurbuz4, Cagri Bilgic4, Canfeza Sezgin6, Kerim Kim Kaban5, Serpil Yilmaz7, Zeliha Yazici8

1Department of General Surgery, NPO Center for Peritoneal Surface Malignancies, Istanbul, Turkey; 2Department of General Surgery, Istanbul Haseki Education & Research Hospital, Istanbul, Turkey; 3Department of Anesthesiology; 4Department of General Surgery, American Hospital, Istanbul, Turkey; 5Department of Medical Oncology, Faculty of Medicine, Biruni University, Istanbul, Turkey; 6Department of Pathology, American Hospital, Istanbul, Turkey; 7Department of Pharmacology, Faculty of Medicine, Biruni University, Istanbul, Turkey

Contributions: (I) Conception and design: E Canbay; (II) Administrative support: E Canbay, Z Yazici; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: B Canbay Torun, K Cosarcan, C Altunal, B Gurbuz, C Bilgic, K Kim Kaban, S Yilmaz; (V) Data analysis and interpretation: E Canbay, S Yilmaz, C Sezgin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Emel Canbay, MD, PhD. Professor of General Surgery, Department of General Surgery, NPO Center for Peritoneal Surface Malignancies, Istanbul, Turkey. Email: drecanbay@gmail.com.

Background: Gastric cancer (GC) with peritoneal metastases (PM) has a dismal prognosis and to date only a few management options have been reported. Of those, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) after induction bidirectional intraperitoneal and systemic chemotherapy (BIPSC) appear as a promising treatment option for these patients. Outcome data including safety and efficacy of CRS with radical Gastrectomy and HIPEC after response to combination of laparoscopic HIPEC (LHIPEC) with BIPSC as an induction therapy in patients with PM of GC was evaluated in this retrospective observational study.

Methods: Diagnostic Laparoscopy was performed in 53 patients with PM of GC who admitted to the Center for Treatment of Peritoneal Surface Malignancies, Istanbul, between 2013 and 2016. Peritoneal cancer index (PCI), ascites status and cytology were determined. The patients underwent LHIPEC and then, BIPSC induction chemotherapy using intraperitoneal docetaxel (30 mg/m2) and cisplatin (30 mg/m2) and intravenous Docetaxel/Cisplatin/5-Fluorouracil (DCF) for 3 cycles. In selected patients, CRS with radical gastrectomy and HIPEC were performed after the response to induction therapy. BIPSC was continued for 3 more cycles with a dose reduction in an adjuvant setting.

Results: All LHIPEC procedures were uneventful with Grade 1–2 side effects (11/53, 20.8%). As a response to induction chemotherapy PCI was reduced from 19.6±8 (range, 6–39) to 13.6±9.8 (range, 1–39) (P<0.001). Ascites was detected in 55% (29 out of 53) and cytology was positive in 51% (27 out of 53) of the patients before induction chemotherapy. Ascites was completely abolished and all cytology became negative. Then, 34 of 53 (64.15%) patients underwent CRS with radical gastrectomy and HIPEC. CC0/1 resection was achieved in 22 (64.70%) patients (P<0.05). The median survival time was 18.9±13.4 (95% CI: 15.2–22.6 months. Combined surgery and HIPEC related mortality occurred in 1 out of 34 patients (2.9%) due to developed diffuse intravascular coagulation at postoperative day 2. Grade 2 operative complications included biliary fistula in one, and duodenal stump leakage in two patients (8.7%). All of the fistula closed with conservative management. The median survival time was 18.9±13.4 months and the median progression-free survival time was 15.6±12.9 with 1-, 2-, and 5-year survival rates of 82.4%, 59% and 17.6% in patients with PM of GC. Multivariate analysis identified high peritoneal cancer index (P=0.000) and complete resection (P<0.05) as independent predictors for better progression-free and overall survival.

Conclusions: The best outcomes can be expected with optimal cytoreduction and limited peritoneal dissemination in response to induction chemotherapy. Knowledgeable selection of patients with PM of GC...
Introduction

The prognosis of GC patients with PM is poor and survival is limited to several months (1, 2). To date, four different strategies for management of PM of GC are currently in use worldwide. The first standard of care for the patients with PM of GC is systemic chemotherapy to achieve control of PM or best supportive care suggested by National Comprehensive Cancer Network (NCCN) guidelines (3). NCCN Guidelines also accept that positive peritoneal cytology during staging laparoscopy or laparotomy is classified as having Stage IV incurable disease (3). If the disease appears to be controlled by radiological evaluation in response to systemic chemotherapy, surgery may be performed to relieve symptoms such as intestinal obstruction in a palliative setting.

A second option is CRS (4) with radical gastrectomy and HIPEC (5). This strategy has been shown to improve survival in a randomized controlled trial (6).

A third approach published by our group presents the outcomes of response to bidirectional intraperitoneal and systemic induction chemotherapy (BIPSC) followed by CRS and HIPEC from 194 patients with PM of GC in 2014 (7). Our results indicated that BIPSC allows one to perform CRS and HIPEC. With complete cytoreduction, prolonged life and even cure of these patients with acceptable morbidity and mortality was reported. Median survival was 18 months. Of those patients who had a CRS and HIPEC, median survival was 15.8 months. More recently, the results of this approach to treatment without HIPEC have been published by Ishigami and his multi-institutional team (8).

The best outcomes in cancer treatments only occur with complete resection. Therefore, to downstage the “Peritoneal Cancer Index (PCI)” (9) or in another words “reduce tumor burden” is an important step to achieve complete cytoreduction for longer survival and even cure of these patients.

A fourth approach is focused on a decreased tumor burden as measured by a reduced PCI using induction chemotherapy administered as LHIPEC (10). Then LHIPEC, in conjunction with BIPSC, was introduced in order to prolong survival as a consequence of decreased tumor burden and reduced ascites formation and to obtain a cytology free from cancer cells (11). Our previous results supported that LHIPEC, (I) had a direct effect on ascites in patients with PM of GC, (II) had a direct effect on positive cytology and (III) had an effect to downsize the tumor.

Here, we report outcome data of surgery with radical gastrectomy and HIPEC after response to LHIPEC and BIPSC induction therapy in patients with PM of GC. Treatment was completed by applying three cycles of BIPSC in an adjuvant setting. We present the following article in accordance with the STROBE Reporting Checklist (available at http://dx.doi.org/10.21037/jgo-20-121).

Methods

Patients

Fifty-three patients with GC admitted to Peritoneal Surface Malignancy Center in Istanbul underwent diagnostic laparoscopy between April 2013 and January 2017. Patients eligible for treatments had (I) a PM of GC confirmed by histopathology, (II) absence of extra-abdominal metastasis and liver metastasis, (III) performance status (Eastern Cooperative Oncology Group (ECOG)) ≥2, (IV) PM were considered as synchronous to the primary tumor if it was diagnosed within 6 months even if patients had prior surgery without GC surgery and systemic chemotherapy for GC. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Biruni University and informed consent was taken from all the patients.

Laparoscopic HIPEC

Initially, diagnostic laparoscopy was performed and
peritoneal biopsy along with peritoneal washing for cytology and ascites’ samples were taken to confirm diagnosis. Peritoneal Cancer Index (PCI) was (9) calculated prior to LHIPEC procedure. All LHIPEC procedures required a five-port technique. Two inflow catheters were placed to subdiaphragmatic spaces and two outflow catheters were placed at the Douglas pouch. HIPEC was performed intraperitoneally (IP) with docetaxel (30 mg/m$^2$) and cisplatin (30 mg/m$^2$) with a total volume of 1.5 L/m$^2$ of saline solution for 90 minutes with inflow temperature of 43 °C. Then, an intraperitoneal port catheter into the upper abdomen and systemic port catheters were placed before termination of the procedure.

**Bidirectional intraperitoneal systemic chemotherapy (BIPSC)**

Three cycles of BIPSC was initiated one week after LHIPEC as a neoadjuvant treatment. Also, every three weeks after cytoreductive surgery (CRS) and HIPEC in an adjuvant setting. BIPSC was a combination of Docetaxel/Cisplatin/5-Fluorouracil (DCF) regimen given systemically plus docetaxel (30 mg/m$^2$) with cisplatin (30 mg/m$^2$) in a 500 mL saline solution administered IP.

**CRS and HIPEC procedure**

Radical Gastrectomy with peritonectomy procedures were performed in patients who responded to induction therapy. After surgery, extensive intraperitoneal lavage (EIPL) was performed as described previously (12). Surgical approach involves radical gastrectomy and D2 lymph node dissection (13), peritonectomy procedures and visceral resections as described by Sugarbaker (14) and Yonemura (15). The epigastric peritonectomy includes to excision of prior midline incision scar and underlying fatty tissue. Bilateral anterior parietal peritonectomy included Morrison’s pouch and peritoneum of right and left paracolic gutter. Omental bursectomy included the peritoneum covering the hepatoduodenal ligament. Bilateral hemidiaphragmatic peritonectomies were performed, if necessary. Cholecystectomy and appendectomy were also performed. If the tumors were within the cul-de-sac, pelvic peritonectomy with total abdominal hysterectomy and bilateral oophorectomy and rectosigmoid colon resection with anastomosis were included to the surgery.

HIPEC procedure was performed with closed technique. Two indwelling catheters were placed to right and left subdiaphragmatic areas and two outflow catheters were inserted into the Douglas pouch. HIPEC was performed with docetaxel (30 mg/m$^2$) and cisplatin (30 mg/m$^2$) with the chemoperfusate heated to achieve a temperature of 43 °C (7). As described by Van der Speeten et al. 260 mg/m$^2$ of sodium-2-mercaptopoethane sulfonate (MESNA) was administered as an intravenous bolus in 100 mL of 0.9% NaCl 15 minutes prior to intravenous initiation of ifosfamide, then repeated 4 and 8 hours later. An intravenous infusion of ifosfamide (1,300 mg/m$^2$) in 1 L of 0.9% NaCl was begun at the initiation of HIPEC and continued at a constant rate over the next 90 minutes (16). Ifosfamide with MESNA as a protective agent was used systemically for 90 minutes.

**Evaluation of treatment**

The patients’ responses to BIPSC were evaluated according to response evaluation criteria in solid tumors (RECIST) criteria with computerized thoraco-abdominal tomography (CAT) scan and with tumor markers CEA, CA19-9, CA72-4, and CA 125 levels (17). The patients with good performance status were assessed by a second diagnostic laparoscopy if radiologic signs and tumor marker levels were clearly decreased or there was no clear evidence of progression. If PCI levels were decreased and washing cytology was free from cancer cells, the patients underwent CRS with radical gastrectomy and HIPEC procedure. PCI levels were calculated by the surgeon (E.C.) and the assistant for each case to address potential sources of bias

The same BIPSC protocol was restarted in three weeks after surgery for 3 cycles with appropriate dose reduction due to postoperative decrease in chemotherapy tolerance. Preoperative, perioperative and postoperative data were collected from electronic medical records. Follow-up was performed by surgeon and medical oncologists.

The first evaluation of early outcome was 7 and 30 days morbidity and mortality after CRS and HIPEC procedures. Surgical complications were graded by the Clavien-Dindo classification system and reported as minor (Grade I and II), major (Grade III and IV) and death (Grade V) (18). Adverse events related to chemotherapy drugs were classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 defined by the National Cancer Institute (19).

The residual disease following CRS was classified intraoperatively using the completeness of cytoreduction (CC) scores (9). Pathological responses were evaluated...
Statistical analysis

The study size was calculated with power analysis. No patients were lost to follow up. Outcome data were obtained from medical records and patients’ interviews. Results are presented as the median with range. The patients who underwent CRS and HIPEC and patients with no further surgery were compared by Fisher’s exact test or Pearson’s chi-square test. Univariate analysis was performed using the log-rank test, multivariate analysis was conducted using the Cox proportional hazards model. Overall survival was calculated by the method of Kaplan-Meier method from the initial date of the treatment to the occurrence of the event or to date of the most recent follow up visit. The overall survival rates were compared between groups of patients who underwent CRS and HIPEC after response to induction chemotherapy and those who did not have further surgery. The extent of peritoneal metastasis (PCI) and completeness of cytoreduction (CC) status was used to assess these groups. Results were compared with log-rank test. Statistical analysis was performed using SPSS 11.0 from Statistical Package for the Social Sciences Inc. software package.

Results

There were 20 male and 33 female patients with a mean age of 51±1.6 (29.0–73.0) years. Histopathological evaluation of PM of GC showed that poorly differentiated and signet ring cell carcinoma were dominant (50/53, 94.3%). Our treatment algorithm for Management of Patients with PM of GC is shown in Figure 1. Of these patients, 16 of 53 patients (30%) had previous surgery within 6 months and 30 of 53 (57%) patients had previous cisplatin-based systemic chemotherapy for a median of 8 cycles. The patients’ characteristics at the beginning of the treatment are presented in Table 1.

LHIPEC

All 53 patients underwent to LHIPEC. At laparoscopy, peritoneal specimens were taken for confirmation of diagnosis. PCI was calculated as 19.6±8 at the beginning of treatment varying between 6–39. Ascites were detected in 29 out of 53 (55%) and cytology was positive in 27 out of 53 (51%) patients. Time between diagnosis and performance of LHIPEC was 11±10 week. No patients were converted to laparotomy, all

Figure 1 Proposed management algorithm of GC patients with cytology positive or with peritoneal metastases.
procedures were uneventful. Grade I–II toxicity following LHIPEC with no mortality was experienced. Patients are discharged 5 to 7 days postoperatively.

**Toxicity of bidirectional intraperitoneal and systemic chemotherapy (BIPSC)**

Adverse events were graded according to the National Cancer Institute- Common Terminology Criteria for Adverse Events Version 4. Hematologic complications were experienced in 2 patients (3.7%) (leucopenia in 2 patients), diarrhea in 1 (1.8%), fatigue in 4 (7.5%) and emesis was experienced in 4 (7.5%) patients. Renal failure was not detected in any of the patients in the induction therapy.

**Port-related complications**

Intraperitoneal port was placed subcutaneously in the lower abdomen. In a single patient the subcutaneous port was turned upside down and needed to be revised.

**Results of LHIPEC and BIPSC**

Sixteen out of 53 patients (31%) had a previous surgery within 6 months. These patients were accepted as a synchronously peritoneal metastases (PM) for this study. Pathological diagnosis was confirmed as peritoneal metastasis of GC in all patients. Ascites resolved and cytology became negative in all 53 patients. Therefore, selection of patients for surgical intervention was made according to decrease in PCI levels, disease stability and patients’ performance status. **Table 2** shows the results of the patients who had the responses to induction chemotherapy.

**CRS and HIPEC procedures**

Thirty-four of 53 patients (66%) underwent total gastrectomy with D2 lymph node resection and peritonectomy procedures. Of those patients, 20 were female and 14 were male. Cytology was negative and ascites absent in these 34 patients. Pathological partial response less than 50% were detected in all patients. There were no complete responses or negative lymph nodes at final pathology report. Radical gastrectomy was performed with CRS. Splenectomy was added in 11 (34%) cases due to heavily involvement of splenic hilum. Subtotal colon resection and segmental small bowel resections were performed in 6 patients (17.6%). Perioperatively, no major complication was experienced and blood loss was minimal. Postoperative complications included gastrointestinal fistula in 3 patients and DIC in one patient. After surgery, 22 patients out of 34 patients (64.7%) had no residual tumor (CC0/1).

Mortality rate was 2.9% (1/34). The cause of death was disseminated intravascular coagulation (DIC) of unknown cause. The patient died on postoperative day 2. Grade II morbidity rate was 8.7%. One had a bile fistula and two had leakage from the duodenal stump. There was acute kidney injury in 8 out of 35 patients (22.85%) that resolved without intervention. Early postoperative hydration resolved the increased creatinine levels by postoperative day 4. Median discharge day was day 12 and ranged between 9–20 days. **Table 2** shows the characteristic of the patients underwent surgery or no surgery in response to induction chemotherapy.

**Survival rates**

**Figure 2** shows the overall survival in patients who underwent surgery with HIPEC after induction chemotherapy and those who had induction chemotherapy alone. In 34 patients with response to LHIPEC and BIPSC, CRS with radical gastrectomy and HIPEC had significantly better overall survival than that those have no response to induction chemotherapy. The median survival time (MST) of 53 patients was 18.9±13.4 months (95% CI: 17.7–24.7 months). The patients’ survival was categorized according to PCI levels and completeness of surgery. 268 patients with response to induction therapy who underwent CRS with radical gastrectomy and HIPEC had significantly better overall survival than those who did not have surgery (21.2 vs. 15.9 months with 1-, 2-, and 5-year survival rates of 82.4% vs. 59%, 17.6% vs. 52.6%, 26.3% vs. 0%, respectively). Patients who had complete CRS (CC0/1) also had a significantly longer survival than those with CC2/3 resection (P<0.009) (**Table 3, Figure 2**). Patients with PCI

---

**Table 2** Response to induction chemotherapy was significant when evaluated by peritoneal cancer index decrease, regression of ascites and conversion to negative cytology

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Before induction chemotherapy</th>
<th>After induction chemotherapy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>19.6</td>
<td>13.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Ascites</td>
<td>29/53 (54.7%)</td>
<td>Absent</td>
<td>0.000</td>
</tr>
<tr>
<td>Cytology</td>
<td>27/53 (50.9%)</td>
<td>Absent</td>
<td>0.000</td>
</tr>
</tbody>
</table>
≤6 had a longer survival than those with PCI >6 (P=0.000) (Table 3, Figure 3).

Discussion

In the current study, 34 out of 53 (64.15%) patients with PM of GC underwent conversion surgery with HIPEC after response to induction chemotherapy. LHIPEC and aggressive surgery with more than 2 anastomoses in combination with HIPEC was performed safely. Twenty-two patients (64.7%) had a CC0/1 resection. Six out of 34 (17.6%) patients showed reach to 5-year survival (Table 2).

The median survival is limited to months without any treatment of patients with GC. Systemic chemotherapy is well established and recognized by NCCN as treatment of PM of GC. Although many chemotherapy trials have been studied for advanced GC, none of them give an optimal treatment with acceptable toxicity (20). Recently, studies based on the effects of surgery in response to induction chemotherapy have attracted surgical oncology groups.

One of those, the GYMSSA study, was a prospective randomized trial to compare a promising new systemic chemotherapy regimen to CRS with HIPEC followed by systemic chemotherapy for PM of GC (21). The systemic chemotherapy used in both arms was FOLFOXIRI (irinotecan, leucovorin, oxaliplatin, and 5-FU). Patients in the standard therapy arm were administered systemic chemotherapy every 14 days for 12 cycles. The patients in the second treatment arm (GYMSSA) underwent gastrectomy, metastasectomy of liver or lung if needed.
and HIPEC. HIPEC was administered with oxaliplatin 460 mg/m² at 41 °C for 30 minutes. Bidirectional treatment using 5-FU 400 mg/m² and leucovorin 20 mg/m² was given just prior to perfusion to enhance the effects of intraperitoneal oxaliplatin. Patients were then started on FOLFOXIRI 8 weeks after surgery. Median survival in the systemic chemotherapy arm was 4.3 months and the GYMSSA arm 11.3 months with 4 of 9 (44%) patients living longer than 12 months.

However, there is not an established role of surgery in PM of GC. Recently, REGETTA trial indicated that tumor burden reducing surgery with combination of chemotherapy was also not superior to chemotherapy alone in advanced GC cases (22).

In comparison to these results, conversion surgery after response to bidirectional chemotherapy was performed in GC patients with PM or positive cytology by Ishigami and his colleagues (23). Their results showed that surgery was safe with longer survival. Then, Okabe and colleagues (24) reported that bidirectional chemotherapy using S-1 with cisplatin had a response rate 57.9% of the patients with PM of GC. These studies provide the rationale of our studies that use direct application of chemotherapy into the peritoneal space. Previously, we reported that the bidirectional chemotherapy with cisplatin and docetaxel had effects on cytology, ascites status and PCI (7). We have also studied in vivo pharmacokinetics of docetaxel in 11 patients (25). Our study identified that docetaxel effectively penetrated the peritoneal nodules up to 1.47 mm in diameter. The area under the curve of docetaxel administered intraperitoneally was almost 13–27 times higher in the peritoneal cavity than systemic administration (26).

Cisplatin (cis-diaminedichloroplatinum-III) causes apoptotic cell death by formation of DNA adducts (27). Platin analogs enters the peritoneal nodules by simple diffusion and penetrates 1 or 2 mm (28). In the setting of CRS and HIPEC, Urano and coworkers (29) showed an excellent in vitro and in vivo thermal augmentation of intraperitoneal cisplatin as well. The combination of cisplatin with docetaxel is expected to be more effective than each one alone. Safety and efficacy are well defined. Cisplatin and docetaxel were selected for intraperitoneal chemotherapies in our study. The combination chemotherapy regimen would be expected to be more effective for PM in intraperitoneal treatment due to higher concentration and augmentation by heat.

Our previous results showed that the ascites formation and peritoneal free cancer cells were abolished and PCI levels were decreased with intraperitoneal-based BIPSC (7). More recently, Ishigami and his group (30) also reported that surgery could be possible in 65% of cases after response to bidirectional induction chemotherapy with paclitaxel and S-1. The Phoenix-GC trial was designed to establish the superior effect of intraperitoneal chemotherapy over the systemic chemotherapy on survival, response rate and safety. However, this trial failed to show superiority in survival of intraperitoneal plus systemic chemotherapy to standard systemic chemotherapy (8). In contrast to this trial result, Zhao and his colleagues (31) identified that survival was significantly longer in multi-modality treatment group compared to systemic chemotherapy group.

Diagnostic laparoscopy is an important diagnostic tool to select patients who have a disease treatable by surgery and to demonstrate the cytology positivity in advanced GC patients (32). Adding HIPEC to laparoscopy converts the diagnostic tool to the therapeutic tool at the same time. LHIEPC is also useful for alleviation of malignant ascites (33-35). Ascites and free peritoneal cancer cells were completely abolished in all our cases with initiation of induction therapy using LHIEPC.

We selected three cycles of bidirectional chemotherapy for our clinical study. It is possible that repeating...
intraperitoneal chemotherapy more than four times could increase the risk of intraabdominal complications such as fistula, adhesions and intestinal obstruction.

There are some limitations of this study. (I) This study has been presented in the form of an observational retrospective study. Therefore, selection bias may be present in this study. Our future goal should be to perform this study with a larger and more structured prospective international collaborative randomized controlled trial. (II) A third arm needs to be added as systemic chemotherapy alone for internal control without induction chemotherapy. (III) Sample size of this study is not adequate to draw final conclusions.

Conclusions
The combination of intraoperative HIPEC with CRS after response to induction LHIPEC chemotherapy may offer superior clinical management favoring their postoperative recovery, a low incidence of complications and improved survival. The best outcomes can be expected with optimal cytoreduction and limited peritoneal dissemination after response to induction chemotherapy. Therefore, highly selected patients with PM of GC seem to be essential to perform conversion surgery with HIPEC safely and with acceptable mortality and morbidity. Limited survival and dismal prognosis in patients with PM of GC requires comprehensive multimodality treatment plans in order to improve the prognosis and survival.

Acknowledgments
We would like to acknowledged with gratitude, the endless support of Yutaka Yonemura.
Funding: None.

Footnote
Provenance and Peer Review: This article was commissioned by the Guest Editors (Paul H. Sugarbaker and Kurt van der Speeten) for the focused issue “Intraperitoneal Chemotherapy for Peritoneal Metastases: HIPEC, EPIC, NIPEC, PIPAC and More” published in Journal of Gastrointestinal Oncology. The article was sent for external peer review organized by the Guest Editors and the editorial office.

Reporting Checklist: The authors have completed the STROBE Checklist. Available at http://dx.doi.org/10.21037/jgo-20-121

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-121). The focused issue was sponsored by the Peritoneal Surface Oncology Group International (PSOGI). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Biruni University and informed consent was taken from all the patients.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References


29. Urano M, Kahn J, Kenton LA. The effect of cis-diamminedichloroplatinum (II) treatment at elevated
