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8. The role of surgery in the management of high-risk gestational trophoblastic neoplasia

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Abstract. Despite the success of chemotherapy in inducing remission in most patients with high-risk gestational trophoblastic neoplasia (GTN), surgical procedures often play an important role in the management of these patients. Approximately one half of patients with high-risk GTN will require some form of surgical procedure during the course of therapy to either remove disease or treat complications. Adjuvant surgical procedures, especially hysterectomy and pulmonary resection, are used most frequently to remove foci of chemotherapy-resistant disease in patients with persistent or recurrent GTN. Conservative resection of chemotherapy-resistant disease within the myometrium may be considered in highly selected patients with no other evidence of disease who wish to preserve fertility. Surgery may also be required in the therapy of patients with high-risk GTN as a means of controlling hemorrhage or dealing with other life-threatening complications.

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Introduction

Despite the success in inducing remission in most patients with gestational trophoblastic neoplasia (GTN), surgical procedures play an important role in management [1]. Approximately one half of patients with high-risk GTN (FIGO stages II – IV, score $\geq$ 7) will require some form of surgical procedure during the course of therapy to either remove disease or treat complications. Adjuvant surgical procedures may be employed to: (1) remove resistant/persistent disease in the uterus or at metastatic sites, (2) decrease tumor burden in the uterus in patients with limited metastatic disease, (3) control tumor hemorrhage, (4) relieve bowel or urinary obstruction, or (5) treat infection [2-5].

In a series of 50 patients with high-risk GTN treated with etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMA-CO) as primary or secondary chemotherapy at the John I. Brewer Trophoblastic Disease Center of Northwestern University between 1986 and 2005, 24 (48%) underwent 28 adjuvant surgical procedures [6]. The procedures included hysterectomy (17), lung resection (5), salpingectomy (1), uterine wedge resection (1), small bowel resection (1), suturing of the liver or uterus for bleeding (2), and uterine artery embolization (1). Twenty-one (87.5%) of 24 patients who had surgical procedures as part of their treatment for high-risk GTN survived. Fifteen (88%) of 17 patients who underwent hysterectomy, 4 (80%) of 5 patients who had resistant foci of choriocarcinoma in the lung resected, all 4 of the patients who had suturing of the uterus, uterine artery embolization, small bowel resection or salpingectomy for bleeding, as well as the patient who had uterine wedge resection of resistant choriocarcinoma survived. This series demonstrates that adjuvant surgical procedures, especially hysterectomy and pulmonary resection for chemotherapy resistant disease as well as procedures to control hemorrhage, are important components in the management of high-risk GTN.

Hysterectomy

Hysterectomy has an important role in the management of high-risk GTN. Primary hysterectomy may be considered in selected patients with high-risk metastatic disease who have small extrauterine tumor burdens and do not desire to maintain fertility, but in general the procedure is not as beneficial as in patients with nonmetastatic and low-risk metastatic disease. The two most frequent indications for hysterectomy are to remove chemotherapy-resistant disease in the uterus and to control excessive uterine bleeding.

High-risk patients with evidence of uterine disease, but no or very little extrauterine disease, may benefit from hysterectomy. Lurain et al from the

Brewer Trophoblastic Disease Center reported that 12 (86%) of 14 patients who had hysterectomy for resistant choriocarcinoma survived [6]. Mutch et al reporting curing 10 (71%) of 14 patients who underwent hysterectomy as part of treatment for recurrent GTN at the Southeastern Regional Trophoblastic Disease Center [7]. The Sheffield, U.K., Trophoblastic Disease Center reported that 9 (75%) of 12 patients who underwent hysterectomy because of chemotherapy-resistant uterine disease had a complete clinical response to surgery [8]. The Charing Cross Hospital, London, U.K., group reported using hysterectomy in 9 of 20 patients who developed resistance to EMA-CO after other chemotherapy [9].

The Sheffield group recently updated their data on the role of hysterectomy in managing persistent GTN at their institution [10]. Of 8,860 registered patients, 62 (0.7%) underwent hysterectomy for GTN: 22 (35.5%) for resistance to chemotherapy and 21 (33.9%) for major hemorrhage, while the remainder had hysterectomy as part of their primary treatment for other indications. The overall remission rate in these patients was 93.5%, however, 7 relapsed and 4 (18%) of 22 patients with resistant disease subsequently died.

Deumplis, et al reviewed the role of hysterectomy in the management of 25 patients with GTN at the Charing Cross Trophoblastic Disease Center over a 13-year period [11]. Histology was choriocarcinoma in 9, placental site trophoblastic tumor in 6, and hydatidiform mole in 10. The two main reasons for surgery were chemoresistance during initial treatment and relapse after treatment. Postoperative chemotherapy was given to 21 of the 25 patients, although the hysterectomy appeared to be therapeutic as demonstrated by a rapid return of hCG levels to normal in 22 of the 25 patients. Survival was 88% (22/25). Of the 3 patients who died, all had high-risk, metastatic disease, one of whom had a placental site tumor.

Cagayan and Magallanes from the Philippines performed adjuvant hysterectomy in 129 (32%) of 420 patients managed with GTN at their institution [12]. Indications for hysterectomy were: uterine rupture (31, 24%), vaginal bleeding (13, 10%), chemotherapy resistance (11, 8.5%), and adjuvant therapy at the beginning of treatment to reduce chemotherapy when future pregnancy was not desired (74, 57.4%). The overall survival was 98.4%, with 2 of the 11 patients who had hysterectomy for chemotherapy-resistant disease dying.

Although hysterectomy clearly has a place in the management of high-risk GTN, it is not often indicated in the primary management of patients with widely metastatic disease unless there is a very large uterine tumor causing bleeding in a patient with no desire to maintain fertility. It is also less common to see refractory disease only in the uterus with the use of current multi-agent chemotherapy. Before deciding to perform a hysterectomy for chemotherapy-resistant high-risk GTN, it is imperative to document the

presence of uterine disease by scans. In the series from the Brewer Center [6] and the Southeastern Regional Center [7], histologic evidence of uterine disease was found in 79% and 83%, respectively, of hysterectomies done for treatment of recurrent or persistent high-risk GTN.

Pulmonary resection

Resection of isolated pulmonary metastases via thoracotomy or thoracoscopy in patients with drug-resistant GTN may be successful in inducing remission. Before performing pulmonary resection, it is important to exclude disease elsewhere as thoroughly as possible with computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, chest, abdomen and pelvis. Tomada et al reviewed their results from planned resection of pulmonary nodules in GTN and proposed guidelines for successful resection: (1) good surgical candidate; (2) primary uterine malignancy controlled; (3) no evidence of other metastatic sites; (4) solitary pulmonary lesion; (5) hCG level < 1,000 mIU/mL. In their series, 14 (93%) of 15 patients who satisfied these criteria were cured by pulmonary resection as compared to none of the patients who had $\geq$ 1 unfavorable factors [13].

Xu et al from Beijing, China reported 50% survival with resection of pulmonary metastatic choriocarcinoma in 43 drug-resistant patients. They noted improved survival in patients who had a solitary lung lesion without metastases to other organs as well as prior good response to chemotherapy [14]. Several U.S. trophoblastic disease centers have reported successful outcomes with pulmonary resection in the management of patients with high-risk GTN. Lurain et al from the Brewer Center reported curing 4 (80%) of 5 patients who had pulmonary resections for drug-resistant disease [6]. Mutch et al from the Southeastern Regional Trophoblastic Disease Center reported that 4 (44%) of 9 patients who underwent thoracotomy with pulmonary wedge resection of resistant choriocarcinoma survived [7]. Fleming et al from the New England Trophoblastic Disease Center reported that thoracotomy was successful in eradicating drug-resistant pulmonary disease in 10 (91%) of 11 high-risk patients. Of the patients who survived, only one had disease outside the lung (brain metastasis) at the time of thoracotomy, and all had solitary lung nodules and hCG levels below 1,500 mIU/mL [15]. It has been noted by several groups of investigators that prompt hCG regression within 1 – 2 weeks of resection of an isolated pulmonary nodule predicts a favorable outcome [4,13,14,16].

Local uterine resection

Conservative resection of chemotherapy-resistant GTN within the myometrium may be considered in highly selected patients with no evidence

of metastatic disease who wish to preserve fertility. There have been several reports of local myometrial resections for nonmetastatic, chemoresistant GTN [6, 7-21]. One of our patients who had persistent uterine disease after sequential single-agent and EMA-CO chemotherapy without evidence of metastatic disease underwent wedge resection of the right cornual portion of her uterus for choriocarcinoma with negative margins. After surgery, she received 3 cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy. She has remained without evidence of disease since then and has had 2 normal pregnancies delivered by cesarean section [6].

Patients considered for this procedure should be thoroughly evaluated for systemic metastases, and the uterine lesion should be carefully localized by MRI with or without positron emission tomography (PET), color flow Doppler ultrasound or hysteroscopy. Lesions less than 2 – 3 cm in diameter associated with low hCG levels are more likely to be completely excised [18]. Most patients undergoing local uterine resection should also receive chemotherapy.

Procedures for tumor hemorrhage

Surgical procedures may also play a role in therapy for high-risk GTN as a means of controlling tumor hemorrhage or dealing with other life-threatening complications [1,2]. Four of the 50 patients with high-risk GTN who we reported from the Brewer Center required surgical procedures for bleeding. These included suturing of the liver for bleeding metastatic choriocarcinoma, suturing of the uterus for perforating choriocarcinoma, small bowel resection for choriocarcinoma metastatic to the small bowel causing gastrointestinal bleeding, and salpingectomy for ruptured tubal ectopic choriocarcinoma [6].

In the series reported from the Philippines, hysterectomy was indicated for uterine rupture in 31 patients (7.4%) and vaginal bleeding in 13 patients (3.1%) out of 420 patients treated for GTN at their institution. This relatively high rate of hysterectomy (10.5%) for control of uterine bleeding in GTN was explained by the authors as due to delayed referral and improper initial management resulting in more advanced disease at presentation to their center [12].

Selective angiographic embolization of the uterine arteries may also be employed to control uterine or pelvic tumor bleeding in lieu of surgical intervention [22-25]. One of our high-risk patients underwent successful uterine artery embolization for intractable uterine bleeding with preservation of fertility [6]. The Charing Cross Hospital group reported on the use of arterial embolization in 14 patients for control of uterine bleeding associated

with GTN. Hemorrhage was controlled in 11 patients, while 2 patients required hysterectomy and 1 patient underwent uterine artery ligation for persistent uterine bleeding. Five pregnancies, including 3 normal full-term deliveries were achieved in these 11 women [24].

Vaginal metastases in GTN are extremely vascular, friable and capable of inducing severe hemorrhagic complications. While most vaginal metastases respond quickly and completely to systemic chemotherapy, their management often includes surgical and angiographic interventions. Yuigua, et al from Beijing, China reported on 51 patients with vaginal metastases, 18 (35%) of whom had massive hemorrhage. Management in these patients included vaginal packing (16), excision (2), hysterectomy with internal iliac artery ligation (1), and selected angiographic embolization (3) [26]. At the Brewer Center, 13 (36%) of 36 patients with vaginal metastases from GTN had significant bleeding requiring blood transfusion (median 7 units, range 1 – 26 units). Seven of these patients required 1 or more procedures for control of bleeding when vaginal packing was not sufficient, including excision (3) or suturing (7) of vaginal lesions, bilateral internal iliac artery ligation (1), and angiographic uterine artery embolization (1) [27].

Craniotomy may be indicated for acute surgical decompression of brain metastasis in high-risk GTN patients with signs or symptoms of increased intracranial pressure [28-32]. Rustin, et al from the Charing Cross Hospital recommended an approach of early craniotomy with excision of isolated brain lesions combined with systemic and intrathecal methotrexate [28]. By contrast, most trophoblastic disease centers in the U.S. recommend integration of whole brain or steriotactic irradiation into systemic therapy for high-risk GTN with brain metastasis in an attempt to prevent brain hemorrhage, reserving craniotomy for neurologic deterioration [29, 30]. Both approaches seem to have similar efficacy, with about 75-80% of patients presenting with brain metastases and 50% of patients overall with brain metastases from GTN being cured [28-30]. Craniotomy for resection of drug-resistant brain lesions is only rarely performed [28-30]. In general, craniotomy is usually reserved for patients with GTN who require acute decompression of central nervous system hemorrhagic lesions to allow for stabilization and institution of therapy [31, 32].

Conclusions

Intensive multi-modality therapy of patients with high-risk GTN using EMA-CO chemotherapy (or some variation of it) along with adjuvant radiotherapy for brain metastases and surgery for control of hemorrhage results in primary remission rates of 65-80%. Approximately 20 – 35% of

high-risk patients will, therefore, fail first-line therapy or relapse from remission. Most of these patients will have a clinicopathologic diagnosis of choriocarcinoma, a large tumor burden reflected by a high hCG level and multiple metastases to sites other than the lung and pelvis, resulting in very high FIGO scores. Salvage chemotherapy with platinum/etoposide-containing drug regimens often combined with surgical resection of sites of persistent tumor (usually in the uterus or lungs), will results in a cure rate approaching 90% in the high-risk patients.

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