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The Role of Surgery and Radiation Therapy in the Management of Gestational Trophoblastic Disease

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the indications for surgical intervention in the management of patients with hydatidiform moles and malignant GTN in order to choose patients most likely to benefit from these interventions.
2. Discuss the use of radiation in the management of patients with malignant GTN and consider its use as an adjunct to chemotherapy or surgery.

ABSTRACT

The primary management of hydatidiform moles remains surgical evacuation followed by human chorionic gonadotropin level monitoring. Although suction dilatation and evacuation is the most frequent technique for molar evacuation, hysterectomy is a viable option in older patients who do not wish to preserve fertility. Despite advances in chemotherapy regimens for treating malignant gestational trophoblastic neoplasia, hysterectomy and other extirpative procedures continue to play a role in the management of patients with both low-risk and high-risk gestational trophoblastic neoplasia. Primary hysterectomy can reduce the amount of chemotherapy required to treat low-risk disease, whereas surgical resections, including hysterectomy, pulmonary resections, and other extirpative procedures, can be invaluable for treating highly selected patients with persistent, drug-resistant disease. Radiation therapy is also often incorporated into the multimodality therapy of patients with high-risk metastatic disease. This review discusses the indications for and the role of surgical interventions during the management of women with hydatidiform moles and malignant gestational trophoblastic neoplasia and reviews the use of radiation therapy in the treatment of women with malignant gestational trophoblastic neoplasia. ***The Oncologist*** 2010;15:593–600

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Introduction

Hydatidiform moles and malignant gestational trophoblastic neoplasia (GTN) are recognized as relatively uncommon, but potentially devastating, diseases occurring in women of reproductive age. Primary management of hydatidiform moles includes surgical evacuation coupled with close monitoring of serial human chorionic gonadotropin (hCG) values. In patients with malignant GTN, surgery was initially recognized as effective only in the treatment of a few women with nonmetastatic choriocarcinoma or postmolar GTN. Malignant GTN was usually a rapidly progressing lethal malignancy until Li et al. [1] reported the first complete and sustained remission using chemotherapy in a patient with metastatic choriocarcinoma who was successfully treated with methotrexate. Although surgery has assumed a lesser role in the management of malignant GTN, selected surgical procedures remain important in the treatment of individual patients. Radiation therapy has been used to control disease in the central nervous system (CNS), liver, and rarely, at other sites.

Evacuation of Hydatidiform Mole

Dilatation and suction evacuation (D&E) is the preferred technique of molar evacuation. Various other methods include medical induction of labor, hysterotomy, and hysterectomy.

Induction of Labor

Induction of labor for molar pregnancy termination can be achieved by the use of prostaglandins with or without the addition of oxytocin. Oxytocin is used if the pregnancy is >14 weeks' gestation because of the lower amount of oxytocin receptors before this gestational age [2, 3]. Laminaria may be used to assist in cervical ripening. There has been reluctance to recommend labor induction for molar evacuation because of the theoretical risk for trophoblastic deportation and embolization during uterine contractions that might result in distant metastasis.

Tidy and associates retrospectively compared different methods of molar evacuation, reporting that medical induction was associated with higher rates of chemotherapy for postmolar GTN [4]. They attributed this effect to higher rates of incomplete evacuation than with suction D&E. Additionally, Schlaerth et al. [5] reported that the rates of significant hemorrhage and incomplete evacuation were higher after induction of labor than after D&E. Furthermore, all but one of their patients ultimately required suction D&E after induction of labor to complete the evacuation [6]. However, when Flam et al. [7] reviewed the prognostic factors influencing postmolar GTN, they reported that uterine size was more important than the mode of molar evacuation.

Abdominal Hysterotomy

Abdominal hysterotomy was used in the past when suction D&E techniques were not widely available. Acute morbidity, including operative blood loss, is greater than with suction D&E. The vertical myometrial incision used to evacuate the mole usually results in operative delivery for subsequent pregnancies. This is an important consideration because the majority of women with hydatidiform moles are in the prime reproductive age group [6]. In a report of 347 patients with hydatidiform moles, Curry et al. [8] found that only 18 (64%) of the 24 patients with evacuation by hysterotomy entered spontaneous remission, compared with 243 (81%) of the 299 who underwent D&E.

Because of the concerns for greater morbidity and a higher incidence of postmolar GTN, induction of labor and abdominal hysterotomy are rarely used for the primary evacuation of hydatidiform moles [6].

Suction D&E

Suction D&E is a safe, rapid, and effective method for evacuating hydatidiform moles [6]. Pre-evacuation insertion of cervical laminaria may facilitate cervical dilatation in a medically stable patient. The majority of the molar tissue is removed by simply rotating the suction cannula and allowing the uterus to involute during evacuation of the uterine contents. The surgeon can assist in uterine involution by gentle uterine massage during evacuation, which also allows assessment of uterine size during the curettage. The use of a bedside ultrasound unit at the time of suction D&E may further ensure complete evacuation of the uterine contents.

The use of ergotamine in the form of methergine (0.2 mg every 2–4 hours) following evacuation is encouraged. Routine second and third evacuations were often performed in the past, but are discouraged because they do not appear to decrease the risk for postmolar GTN [9] and may result in perforation or uterine senechiae. Anti-D immunoglobulin should be given to Rh^- patients because Rh D factor is expressed in the trophoblast.

In the U.S., sharp curettage is often performed with a large curette to ensure complete uterine evacuation, and this specimen is submitted for separate histological analysis. Rice et al. [10] concluded that the diagnosis of invasive mole or choriocarcinoma is rarely made from the sharp curettings. In their review of pathologic specimens, only one pathologic feature, fibrinoid deposits, identified in sharp curettings was associated with the incidence of persistent GTN. Although 12 of the 25 patients who attained remis-

sion without chemotherapy had fibrinoid deposits in the sharp curettage specimen, they were identified in only one of the eight patients who developed persistent GTN.

Complication rates after suction D&E are higher in uteri of >16 weeks' gestation, including hemorrhage, perforation, and pulmonary complications [11, 12]. Patients with a markedly enlarged uterus should have large-bore i.v. infusion catheters and blood available for transfusion. Central hemodynamic monitoring and provision for immediate laparotomy or laparoscopy during the procedure should also be available [6].

Uterine perforation is a relatively rare complication when suction D&E is used for molar evacuation [6]. Rarely, perforation occurs in a region of deep myometrial penetration by invasive mole or there is active bleeding at the perforation site. Surgical management in these cases should be individualized on the basis of the site and extent of perforation. Repair or resection of the perforation site is usually attempted, but hysterectomy is often required in this setting [6].

In patients who desire retention of fertility and are faced with significant continuous vaginal bleeding after suction D&E, hemorrhage can be controlled by balloon tamponade such as with the Bakri balloon used in postpartum hemorrhages, as reported by Kolomeyevskaya et al. [13]. Uterine artery embolization is another technique that has been used in cases of severe hemorrhage to avoid hysterectomy after excluding uterine perforation as a cause of bleeding.

Hysterectomy

For women who have completed their families and have risk factors for postmolar GTN, hysterectomy offers the advantage of simultaneous evacuation and sterilization [6]. Because malignant sequelae are more prone to occur in older age groups—37.5% of patients aged ≥50 years versus 27.5% of patients aged 40–49 years versus 13.9% of patients aged ≤15 years—after molar evacuation [14], hysterectomy plays a crucial role in the management of these patients and offers a lower risk for malignant sequelae than with suction D&E [15]. Hysterectomy decreases the overall risk for postmolar GTN to approximately 3.5% from the anticipated 20% following suction D&E [8].

Because most women with hydatidiform moles are aged <40 years, the adnexa should not be removed unless the patient has obvious adnexal metastases, is perimenopausal, or has complications related to theca lutein cysts [6]. All patients should be chemically monitored after hysterectomy because it does not completely eliminate the potential for postmolar GTN [8, 15].

Theca Lutein Cysts

Theca lutein ovarian cysts usually are present at the time of presentation in about 25% of patients [16], but can develop after molar evacuation. They are caused by elevated hCG levels [17]. Other signs of ovarian hyperstimulation, such as pleural effusion and ascites, have been documented. The resolution of theca lutein cysts lags behind the drop in hCG values. They may take several months to resolve, but require surgical intervention in only 3% of cases for rupture or torsion [16]. If these are recognized at the time of surgical exploration, aspiration of prominent cysts can be performed.

Surgery Incorporated in the Management of Malignant GTN

The emergence of effective chemotherapy has lessened the importance of surgery for patients with malignant GTN. Hysterectomy may be incorporated into the primary or secondary management of women with GTN [6, 18, 19]. Patients with high-risk GTN often require surgery to address disease complications [6, 19].

Surgical procedures to extirpate sites of disease are often performed during a course of chemotherapy to minimize the possibility of inducing metastases by surgical manipulation of tissues.

Pretherapy D&E

Patients who develop postmolar GTN frequently present with vaginal bleeding and uterine enlargement [6]. The efficacy of a second therapeutic D&E to remove additional trophoblastic tissue and allow spontaneous regression has never been prospectively evaluated. However, several retrospective studies suggest that routine performance of a repeat D&E is not likely to benefit the majority of patients with postmolar GTN [20–22].

Only 20% of 37 patients reported by Schlaerth and colleagues [21] with nonmetastatic GTN had a sustained drop in hCG levels and entered into spontaneous remission after the second procedure. Likewise, others have observed that a second D&E affects management in <10% of patients after primary evacuation of a hydatidiform mole by directly producing remission or providing histological evidence of malignant GTN [20–22]. In contrast, Pezeshki and colleagues evaluated the results of a second uterine evacuation for a presumptive diagnosis of GTN during follow-up in 544 patients after molar evacuation [23]. Among the 282 patients with a second evacuation performed for rising or persistent hCG values, only 40% required chemotherapy. Chemotherapy was more likely when the urinary hCG level was >1,500 IU/l at the time of the secondary evacuation, or if there was histologic evidence of GTN in the curettings.

A second D&E might theoretically reduce the amount of chemotherapy needed to produce remission, if performed immediately prior to treatment, by debulking the intrauterine tumor burden. In a study by van Trommel et al. [22], a median of six cycles of chemotherapy was required in the control group of 209 patients who did not undergo a second D&E, compared with five courses in patients receiving a second procedure ($p = .036$). In a retrospective review of 150 patients treated with methotrexate for low-risk postmolar GTN, however, Growdon and associates [24] found no association between a second D&E and the number of methotrexate courses or the need for alternative chemotherapy regimens.

Repeat curettage may carry a higher risk for complications than primary D&E for molar evacuation. Schlaerth and associates reported an 8.1% incidence of uterine perforation during the secondary D&E among 37 patients who underwent a secondary curettage during the course of treatment for postmolar GTN [21]. Uterine perforations or blood loss >1,000 ml occurred in 4.8% of the 85 patients in the series reported by van Trommel et al. [22], whereas no significant acute complications were reported by Pezeshki et al. [23]. No study to date has investigated the long-term incidence of uterine senechiae after a second D&E.

Most investigators are reluctant to recommend routine pretherapy D&E. However, a few patients require a second D&E before or during chemotherapy because of hemorrhage with anemia or because of infected products of conception.

Hysterectomy for Malignant GTN

The majority of women with malignant GTN can be cured with chemotherapy alone. Hysterectomy, however, continues to play a role in the management of women with malignant GTN.

A 100% sustained remission rate was reported for 194 patients treated for nonmetastatic or low-risk metastatic GTN by Hammond et al. [19]. Of these, 162 wished to preserve fertility and 89% were able to avoid hysterectomy. All 32 women treated with primary hysterectomy combined with single-agent chemotherapy regimens entered sustained remission. When compared with similar patients who had low-risk disease and were treated with chemotherapy alone, patients receiving primary hysterectomy had a shorter duration and lower total dose of chemotherapy, equivalent to one cycle of chemotherapy [19]. In another retrospective study, the total dose of etoposide used for low-risk GTN patients was lower among those with nonmetastatic disease treated with adjuvant hysterectomy than among those treated with chemotherapy alone, again roughly equivalent to a single cycle of chemotherapy. This effect was not observed among the patients with low-risk metastatic disease [25]. Therefore, primary hysterectomy is a reasonable adjunct to chemotherapy for patients with low-risk GTN who do not desire to preserve their childbearing capacity [11].

Additionally, hysterectomy can be employed in patients with nonmetastatic or low-risk metastatic GTN who become resistant to primary chemotherapy, in order to achieve remission without requiring multiagent chemotherapy. As reported by Hammond et al. [19], 13 of 122 patients with nonmetastatic GTN and five of 40 patients with low-risk metastatic GTN who demonstrated failure of remission after chemotherapy were placed in sustained remission after secondary or tertiary hysterectomy. Primary or secondary hysterectomy, however, was not effective in reducing chemotherapy requirements or improving cure rates for women with high-risk metastatic GTN [19]. This likely reflects a greater extrauterine disease burden in these women.

Salvage hysterectomy is an option in producing remission in most patients with chemoresistant nonmetastatic or low-risk metastatic disease [19, 26, 27]. Salvage hysterectomy may be integrated into the treatment of selected patients with high-risk metastatic GTN who have a small extrauterine tumor burden. Patients with recurrent GTN often present with limited extrauterine dissemination and may benefit from salvage hysterectomy [28].

Hysterectomy for GTN treatment can prove very difficult. The uterine vasculature may be very prominent, and enlargement of the uterine venous plexus may lead to hemorrhage during ureteric dissection, particularly in cases in which the tumor has spread beyond the uterus into the parametrium. Temporary ligation of the hypogastric arteries may be helpful in reducing intraoperative hemorrhage [29].

Emergency hysterectomies have been reported in cases of intra-abdominal bleeding or severe vaginal bleeding [30]. In a series of 18 total abdominal hysterectomies, four were performed emergently as a result of uterine perforation resulting in massive hemoperitoneum [31]. Additionally, it is important to emphasize the need for a detailed intraoperative examination after completion of the hysterectomy to exclude or identify any metastatic lesions.

In contrast to gestational choriocarcinoma or postmolar GTN, hysterectomy plays an essential role in the management of placental site trophoblastic tumor (PSTT) because it is much more resistant to methotrexate and dactinomycin chemotherapy. Most patients present with nonmetastatic PSTT. Hysterectomy alone is curative in approximately two thirds of patients [32, 33]. Conversely, hysterectomy is not as beneficial in the management of PSTT patients with widespread metastases.

Conservative Myometrial Resection

Conservative myometrial resection combined with uterine reconstruction might be considered in highly selected patients with nonmetastatic GTN who wish to avoid hysterectomy [34–36]. Kanazawa et al. [34] evaluated 22 patients with local myometrial resection of invasive moles. All patients had lesions localized in the myometrium, defined by pelvic angiography, ultrasound, and computerized tomography techniques. Seven patients required chemotherapy after surgery. They observed that the reproductive performance of patients undergoing myometrial resection was similar to that of patients treated with chemotherapy alone. Any patient considered for this procedure should be carefully evaluated for systemic metastases, and the uterine lesion should be localized by imaging and hysteroscopy. Intraoperative frozen sections should be used to assess surgical margins. Their indications for selecting patients for conservative myometrial resections were: (a) urinary hCG titers <10,000 IU/day, (b) no evidence of pulmonary involvement, and (c) metastases in the lungs, controlled by chemotherapy prior to the operation. They reported that postsurgical chemotherapy might be avoided or reduced if these criteria were fulfilled [34]. An exception to these guidelines is uterine perforation and/or marked uterine hemorrhage resulting from myometrial invasion of a molar trophoblast, for which emergent focal resection may be indicated.

During a hysterectomy or myometrial resection for any of the above indications, ovarian removal is not usually required, because GTN rarely metastasizes to the ovaries and these tumors are not hormonally influenced [6].

Conservative Management of Uterine Rupture

Estrella and Soriano-Estrella [37] reported on two patients with low-risk GTN managed by primary repair of uterine rupture and subsequent chemotherapy, with a documented complete response in one patient, whereas the other was lost to follow-up.

Pulmonary Resection

The most frequently employed surgical procedure for extirpation of extrauterine metastases of GTN is thoracotomy with pulmonary wedge resection. Although this can safely be performed in conjunction with chemotherapy, it is not necessary to resect lung metastases in the majority of patients [6]. Resection of pulmonary nodules in highly selected patients with drug-resistant disease may successfully induce remission after excluding active disease elsewhere [6]. Highly selected patients will require more than one pulmonary resection during the course of treatment in order to achieve a durable remission [26].

Tomoda et al. [38] proposed the following criteria for successful pulmonary resection: (a) the patient must be surgically fit, (b) the primary malignancy must be controlled (the uterus must have already been resected or there must be no radiographic evidence of tumor in the uterine cavity), (c) there must be no evidence of widely disseminated metastatic disease elsewhere in the body, (d) the radiologic evidence of pulmonary metastasis must be limited to one lung, and (e) the urinary hCG value must be <1,000 mIU/ml. Remission was achieved in 14 of their 15 patients who met the above criteria [38].

Craniotomy

Brain metastases occur in 9.3%–21.4% of patients with metastatic GTN [39, 40] and are associated with a worse prognosis than with vaginal or pulmonary metastases [6]. The key factors for a successful outcome in managing these patients are early diagnosis and aggressive therapy. These lesions tend to be highly vascular and have a tendency for central necrosis and hemorrhage. Early deaths are caused by acute hemorrhage, with acute neurological deterioration very early in the course of treatment [39, 40]. Any woman of reproductive age diagnosed with brain metastasis or cerebral hemorrhage should be screened for GTN with a serum hCG test. Tissue confirmation is not necessary for the diagnosis of brain metastasis [6]. In the U.S., brain irradiation has usually been integrated into the treatment of brain metastasis in an attempt to prevent hemorrhage and neurological deterioration [26, 41]. Craniotomy has usually been used only to prevent acute deterioration [19].

Ishizuka et al. [40] concluded, from autopsy studies, that surgical decompression should be performed in any patient with signs or symptoms of increased intracranial pressure, followed closely by multiagent chemotherapy. Furthermore, Rustin and associates [42] recommended early craniotomy with excision of isolated lesions combined with high-dose systemic and intrathecal chemotherapy to treat patients with brain metastases, reporting a 72% sustained complete remission rate. Others have confirmed the feasibility of this approach [43].

Evans et al. [39] demonstrated a similar rate of sustained complete remission in patients who presented with CNS metastasis and who were treated with primary therapy using multiagent chemotherapy consisting of methotrexate, actinomycin D, and chlorambucil or etoposide-based regimens, given with concurrent whole-brain irradiation at a dose of 3,000 cGy in 10 fractions. Intrathecal methotrexate was not used in that series [39]. These reports underscore the value of multiagent chemotherapy and multimodality therapy in the management of metastatic GTN to the brain, using different approaches to avoid early mortality from the CNS lesions.

In patients with drug-resistant brain lesions, it is of vital importance to exclude active disease elsewhere prior to attempting surgical resection because craniotomy in these instances is rarely effective [6].

Surgical Management of Renal Metastases

The incidence of renal metastases is 1%–14% in GTN patients [44]. Soper and associates described eight patients with high-risk clinical factors treated for renal metastasis of GTN, all of whom had pulmonary metastasis [44]. Four patients additionally had CNS disease. Combination chemotherapy, including methotrexate, dactinomycin, and chlorambucil, was given to all patients. Five received etoposide-containing regimens as salvage therapy. None received renal irradiation and five underwent nephrectomies. Three patients in that series survived. All had limited metastatic disease elsewhere [44]. Nephrectomy should be considered only if there is unilateral involvement and limited disease involving the lungs, but may not contribute to survival in patients with extensive systemic disease [44, 45].

Treatment of Metastatic Vaginal Disease

Vaginal metastases of malignant GTN are highly vascular. Biopsy or resection of these lesions should not be undertaken unless they are the only sites of chemoresistant disease. Packing or angiographic embolization are usually used in an attempt to acutely control bleeding during initiation of therapy [6].

Surgical Management of Liver Metastases

Most patients with metastatic liver disease should be managed initially with multiagent chemotherapy. Only rarely will resection of isolated liver metastases be feasible for treatment of drug-resistant disease because most patients will have other sites of active disease, or disseminated involvement of the liver [6].

Involvement of Other Intra-Abdominal Organs

If chemotherapy has not been effective in controlling metastatic sites involving other abdominal or pelvic organs, surgical resection or the application of other procedures is dependent on the organ and the symptoms associated with its involvement. Rarely, intestinal resection is required in cases of gastrointestinal bleeding [19, 46].

The probability of achieving a complete response following various salvage surgical procedures in patients with chemorefractory GTN was evaluated by Lehman and associates [26] in a series of 33 patients. The patients who were successfully salvaged: (a) had one preoperative disease site, (b) underwent salvage surgery within 1 year from the time of initial diagnosis, (c) had pathological specimens with histologic findings other than choriocarcinoma, and (d) had a total World Health Organization score <8.

Conversely, Feng et al. [47] evaluated 61 patients with chemoresistant GTN who underwent various salvage surgical procedures in the course of their management for predictive factors of poor response to surgical management. Patients with PSTT were excluded. The clinical factors predicating failure of salvage surgery were: (a) age >35 years, (B) hCG value >10 IU/L, (c) antecedent nonmolar pregnancy, and (d) metastasis outside the lungs.

Ancillary Procedures

Selective angiographic localization and embolization techniques have been used to conservatively manage hemorrhage from active sites of metastatic GTN and to treat intrauterine arteriovenous malformations that can occasionally develop after treatment of GTN [4]. Grumbine et al. [48] reported prophylactic placement of a catheter in the hepatic artery for balloon occlusion or embolization in the event of rupture in a patient with liver metastases of GTN. Lang [49] used selective catheter placement for chemoembolization in three patients with liver metastases and two patients with pelvic tumors from GTN. All had chemoresistant GTN and relatively localized persistent tumors. Two of the patients with liver metastases achieved long-term remissions, with minimal hematological toxicity. Recently Soper et al. [43] reported a long-term survivor with extensive liver, lung, and brain metastasis from GTN who required embolization of multiple bleeding liver lesions to allow stabilization during initial therapy. A rare case of primary choriocarcinoma of the cervix was also recently described, presenting with massive cervical bleeding that was successfully controlled with selective uterine artery embolization [50].

Radiation Therapy for Malignant GTN

Radiation has a limited but vital role in the management of patients with malignant GTN, frequently used to treat patients with brain or liver metastases in an effort to minimize hemorrhagic complications at these sites. Patients who develop brain metastases while on treatment or relapse in the brain after an initial complete remission represent a group of patients with a worse prognosis than those who present with brain metastases before treatment [39, 51–54]. Whole-brain radiation is usually administered at 2,000–4,000 cGy in 10–20 equal fractions that are given concurrently with combination chemotherapy, with reduced-field boosts given in selected patients. The combination of chemotherapy and radiation is both hemostatic and tumoricidal [55]. Survival rates of 50%–75% were reported in a series of pa-

tients who initially presented with brain metastases and received combined chemoradiation [6].

An alternative approach using high-dose systemic combination chemotherapy and early neurosurgical intervention yields results similar to those with the concurrent chemoradiation approach, as described previously [42, 43]. Concerns about neurocognitive toxicity from concurrent moderate- to high-dose methotrexate and whole-brain radiation therapy have led to adaptation of the above approach to the treatment of CNS metastases at some centers in the U.S. [43].

Barnard et al. [56] reported on 15 patients with liver metastasis receiving whole-liver irradiation concurrently with chemotherapy. Only two (13%) patients survived. In an effort to limit radiation-induced hepatitis, the recommended dose of whole-liver radiation is 2,000 cGy administered over 2 weeks [54, 56]. However, in a series reported by Bakri et al. [57], none of the eight patients treated with methotrexate–dactinomycin–cyclophosphamide combined with whole-liver radiation survived, compared with survival in five of the eight patients treated with etoposide-based combination regimens given without radiation.

Radiation of the kidneys is unlikely to achieve significant disease control for bilateral renal metastases given the low radiation tolerance of the kidneys [44]. Unilateral renal metastasis might be treated with radiotherapy, but the combination of chemotherapy and irradiation was not successful in a patient reported by Mazur et al. [58].

Conclusion

Despite advances in chemotherapy for GTN, surgical procedures and radiation therapy continue to play significant roles in the management of women with hydatidiform moles and malignant GTN. The integration of multimodality treatment, especially in patients with high-risk disease, requires physicians with experience in the treatment of these diseases in order to coordinate all aspects of therapy. Cure rates of 75%–84% for patients with high-risk disease are reported from centers that specialize in the treatment of women with this malignancy.

Author Contributions

Conception/Design: Rabbie K. Hanna, John T. Soper
Provision of study material or patients: John T. Soper
Collection and/or assembly of data: Rabbie K. Hanna
Data analysis and interpretation: Rabbie K. Hanna, John T. Soper
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