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THE ROLE OF SURGERY IN THE MANAGEMENT OF GESTATIONAL TROPHOBLASTIC DISEASE

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21.1 INTRODUCTION

The use of chemotherapy regimens in the management of gestational trophoblastic disease has reduced the need for surgical intervention once the uterus has been evacuated. Chemotherapy produces high cure-rates while maintaining fertility, allowing women to have further pregnancies. While many centres in the developed world pursue this strategy surgery, particularly in the form of hysterectomy, still plays a valuable role in the management of this disease, particularly in areas of high incidence and where resources may be limited.

This chapter will cover the role of surgery in the following:

- evacuation of molar tissue
- GTD affecting the fallopian tube
- the role of hysterectomy
- conservative alternatives to hysterectomy
- surgery for metastatic disease

21.2 EVACUATION OF HYDATIFORM MOLE

21.2.1 Changes in diagnosis

The widespread use of ultrasound in the first and early second trimester of pregnancy has revolutionised the management of molar pregnancies. Soto-Wright et al demonstrated a reduction in the mean gestational age at presentation to the New England Trophoblastic Disease Center from 16 weeks, during the time period 1965-75, to 12 weeks between 1988 –93 [1]. Fowler et al in a review of 1053 women registered at the Charing Cross Hospital Trophoblastic Disease Unit between 2002-5 found the median gestation at registration was 10 weeks [2]. In countries where ultrasound is widely available late presentation of a molar pregnancy is uncommon. Most women now present with minor symptoms such as irregular vaginal bleeding in the first trimester and investigation by ultrasound examination may confirm the presence of a molar pregnancy. In some cases routine ultrasound

examinations, for the purposes of confirming gestational age or antenatal screening, will lead to the diagnosis of asymptomatic molar pregnancy. However the reduction in gestational age at presentation does cause problems with pre-evacuation ultrasound diagnosis of hydatidiform mole. In a review of 155 histologically confirmed complete or partial moles Sebire et al found that in 67% of cases the ultrasound diagnosis prior to uterine evacuation was either that of a delayed miscarriage or an anembryonic pregnancy. When molar disease was expected following ultrasound examination this was confirmed in 84% of cases [3]. This finding was confirmed by Fowler et al in a larger series of patients, only 44% of women with histologically confirmed hydatidiform mole had a correct ultrasound diagnosis prior to evacuation. The diagnosis of molar change improved when the pathological diagnosis was a complete mole compared to a partial mole (79% vs 29%) and there was also a trend of improved ultrasound diagnosis with increasing gestational age, 60% were correctly diagnosed after 14 weeks gestation compared with 35-40% diagnosed before 14 weeks [2].

In summary the gestational age at presentation of molar pregnancy has reduced and increasingly the diagnosis of hydatidiform mole is unexpected prior to histological examination. Therefore it seems prudent to recommend the histological examination of all failed pregnancies.

21.2.2 Complete Moles

The ideal management of complete molar pregnancy is by surgical evacuation using suction curettage [4]. This method will allow a uterus of any size to be evacuated and molar tissue may be easily removed via a suction curettage. Cohort studies of prospectively collected data from Charing Cross and Sheffield Trophoblastic Disease Centre have confirmed the safety of this approach [5,6]. However, women undergoing medical methods of uterine evacuation have a 1.7 – 1.9 fold increased risk for subsequent chemotherapy. This increased risk appears not to be due to excessive uterine enlargement but rather to more inefficient evacuation of the uterus [6,7]. Therefore the use of medical methods should be avoided, if possible, in the management of complete moles. Prostaglandins can be used to prepare the cervix prior to suction evacuation because they appear not to affect the subsequent need for chemotherapy [8]. Oxytocin infusions may be useful in the management of molar pregnancies but ideally should be used once the evacuation has been completed. Oxytocin infusions have been shown to raise intrauterine pressure, which may lead to embolisation of trophoblastic tissue to other organs. This may manifest itself either as an acute event with the collapse of the woman with severe respiratory failure or to an increased risk of requiring subsequent chemotherapy following uterine evacuation.

Very rarely women may present with excessive vaginal bleeding leading to haemodynamic instability and in these cases oxytocin infusions may be required to reduce the bleeding and save life.

21.2.3 Partial Moles

Surgical evacuation for partial molar pregnancy is recommended if this is technically feasible [4]. However the presence of fetal tissue may preclude this method, resulting in the need for medical management. Because of the low risk of chemotherapy following partial molar pregnancies (0.5%), the increased risk associated with medical methods of evacuation does not appear to be significant.

21.2.4 Repeat evacuation of the uterus

The indications for a repeat uterine evacuation in the management of gestational trophoblastic disease are unclear. These procedures are often performed, for persistent heavy vaginal bleeding, by gynaecologists without prior consultation with specialist centres. The Sheffield Centre evaluated the role of repeat evacuation in the management of molar disease. In a study of 4050 women registered at the centre 282 underwent second evacuation when the hCG level was elevated, 60% of these cases did not require any chemotherapy to achieve normalisation of hCG levels. A Monte Carlo analysis of this data suggested a cut off hCG level of 1500 IU/L as the best discriminator as regards the need for subsequent chemotherapy. However, there is considerable heterogeneity in the study population to suggest a level up to 5000 IU/L may influence a response to second evacuation [9]. In a review of 8900 women registered by Charing Cross 444 women underwent second evacuation. 57% of women whose hCG was less than 5000 IU/L prior to the second evacuation did not require chemotherapy [10]. However, a study by van Trommel et al demonstrated only a marginal advantage (9.4%) for women who underwent a second evacuation. This observation may in part be due to differences in the nature of the antecedent pregnancy and the extent of disease spread between the two groups in the study [11]. Women who did undergo a second evacuation require one less course of chemotherapy to achieve remission and second evacuation may therefore help in debulking of the uterine disease. The Gynecologic Oncology Group has recently completed a prospective phase II trial (GOG 242) to address the utility of second evacuation. The primary objective of the trial was to determine the response to second evacuation in patients with GTN with secondary objectives of assessing response in relation to HCG levels, depth of myometrial invasion, size of uterine lesion, F.I.G.O. score and describe the surgical complications. Surgical cure was defined as an absence of rise or plateau of hCG for 6 months post evacuation. The

preliminary data was presented at the Society of Gynecologic Oncology meeting, March 2014. Sixty four patients were recruited with four of these excluded to date. 88% had a complete mole, 8% had a F.I.G.O. score of 5 or 6, 40% had a hCG level $>10^4$ and 7% $>10^5$. One case of uterine perforation was reported and was managed conservatively. The other main complications were associated with haemorrhage, 4 grade 1, 1 grade 2 and 1 grade 3. 23(38%) women were cured and a further 2 (3%) had a complete response but failed to complete follow up. Disease progression occurred in 33 (55%) cases and new metastatic disease was found in two women. In 4 cases the histology from the second evacuation was placental site trophoblastic tumour (PSTT). Further analyses of the secondary objectives are awaited [12].

This prospective trial confirms that there is a role of second evacuation in the management of molar pregnancy and women will avoid the need for chemotherapy. The rate of surgical complications appears to be acceptable. The high incidence of PSTT in the second evacuation was unexpected.

There appears to be no role for considering more than two evacuations as the need for chemotherapy increases with the number of evacuations [9].

21.3 GESTATIONAL TROPHOBLASTIC DISEASE IN THE FALLOPIAN TUBE

Gestational trophoblastic neoplasia can develop following a pregnancy within the fallopian tube. This may occur after a non molar pregnancy or a molar pregnancy. Four series have reported the incidence and management of the condition. The incidence of ectopic GTD in the United Kingdom is low (1.5 per 1,000,000 live births) and the risk factors and the presentation of ectopic GTD is identical to cases of non molar ectopic pregnancy [13].

A major problem with the condition would appear to be over diagnosis by pathologists. In a series of 31 cases registered at the Sheffield Centre 23 underwent histological review and only 6 cases were found to have GTD, 3 early complete moles and 3 choriocarcinomas [14]. Charing Cross found in a series of 132 registered cases of ectopic GTD only 8 confirmed on review, 2 partial, 5 complete and 1 unspecified mole [15]. The cause of the over diagnosis may be the exaggerated features of early placentation [14,15]. This finding was confirmed in a further review of 6,708 women registered at the Sheffield Centre between 1997 and 2010, on the 42 cases registered only 12 had confirmed ectopic GTD, four choriocarcinomas, five partial moles and four early complete moles [16]

In a series of 16 cases of ectopic GTD reported from the New England Trophoblastic Center there were 5 cases of partial mole, 5 cases of complete mole and 6 choriocarcinomas. Only the cases of choriocarcinoma required chemotherapy [17]. In Sheffield 7

women with ectopic GTN have been treated with chemotherapy, five cases of choriocarcinoma, one early complete mole and one case of presumed cornual ectopic GTN. All cases had low risk chemotherapy and are in remission [13,16]. In the Charing Cross series there were no cases of persistent disease [15].

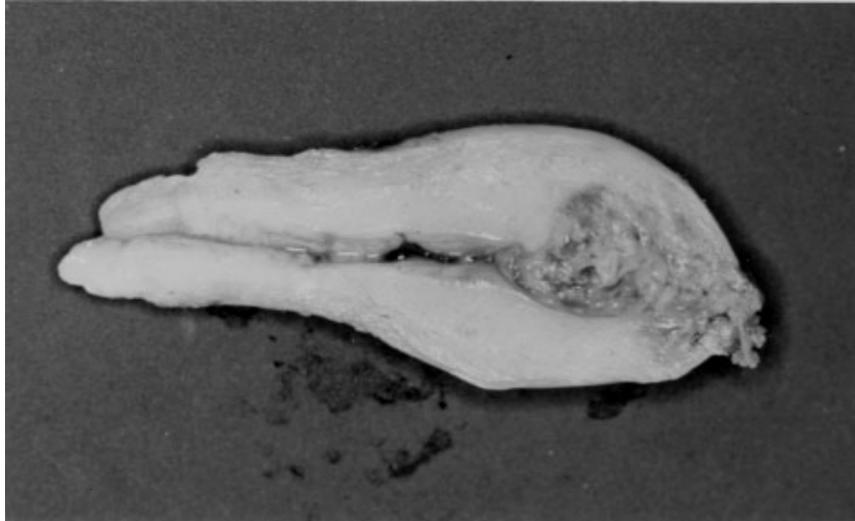
21.4 THE ROLE OF HYSTERECTOMY

21.4.1 Hysterectomy as primary treatment

Hysterectomy in the primary management of hydatidiform mole has been widely advocated and used by many centres. The use of hysterectomy as part of primary treatment is heavily dependent on the availability of healthcare resources. While hysterectomy is a more radical method of evacuating gestational trophoblastic tissue it does not avoid the need for subsequent monitoring and registration of patients. Ideally indications for primary hysterectomy at the time of presentation should therefore include requests for sterilisation or the presence of pre-existing gynaecological conditions for which hysterectomy may be a suitable treatment. However, some older patients may indicate a wish to undergo hysterectomy as the method of evacuation and this is acceptable provided women are made aware of the risks of the major surgery and that there may still be a need for chemotherapy after surgery.

Women with molar pregnancies may suffer from excessive vaginal bleeding either at the time of presentation or after uterine evacuation. Occasionally this bleeding will become life threatening and hysterectomy is a reasonable option particularly for women who have completed their family. Women may occasionally present with severe intra-peritoneal haemorrhage as a result of a penetrative invasive mole leading to uterine perforation. Emergency laparotomy and hysterectomy may be life saving in such situations.

Figure 21.1 Uterus showing penetrative invasive mole which caused severe intraperitoneal hemorrhage.



Perforation of the uterus is a recognised complication of uterine evacuation because the pregnant uterus is much softer compared with the non-pregnant state. Perforation may occur due to the passage of an instrument through the uterine wall or the lower uterine segment/endocervix may tear during manual dilatation prior to suction evacuation. In many cases the perforation at the time of evacuation can be managed conservatively; however surgical repair, including hysterectomy, may be required if there is significant intra-abdominal haemorrhage or vaginal bleeding.

In a review of 8860 patients with GTD registered at the Sheffield Trophoblastic Tumour Disease Centre 62 (0.71%) patients underwent hysterectomy as part of their management. Hysterectomy was part of the primary treatment of GTD for 31 patients. Major haemorrhage was the causative factor for 18(58%) patients and in all cases the operation was performed as an emergency. 13 patients underwent hysterectomy as an elective procedure, of these four patients had a preoperative diagnosis of PSTT and a further two patients had choriocarcinoma. Two patients presented with a pelvic mass on ultrasound examination which following surgery was found to be trophoblastic tumour. Other indications were; one patient requested hysterectomy as prophylaxis against further problems; one patient requested hysterectomy instead of chemotherapy; one patient underwent hysterectomy for residual disease after evacuation of the uterus and one patient underwent hysterectomy for persistent but not life threatening bleeding. The indication was unclear for one patient. Despite the use of hysterectomy, 20(65%) patients required chemotherapy including 15 patients who underwent the procedure as an emergency [18].

Hysterectomy was used frequently in the series reported by the group from Ain Shams University [19]. The overall incidence of hysterectomy was 35% in a total of 120 patients with GTN treated at their Unit. When these patients were stratified according to the NIH classification system, 25% of women with non-metastatic GTN

underwent hysterectomy compared with 82% of women with low risk metastatic GTN and 32% of women with high-risk metastatic GTN. All the women in the non-metastatic group who underwent hysterectomy were cured without need for chemotherapy. All the women in the low-risk metastatic group received single-agent chemotherapy in addition to hysterectomy and all were cured.

In a review of 193 patients with GTN treated at the Philippine General Hospital 116 (60%) underwent hysterectomy. The indication for hysterectomy in 56% of cases was as an adjuvant to chemotherapy [20]. A further study from Poland reported an overall incidence of 29%; 10% of women underwent hysterectomy before treatment and 19% had hysterectomies while receiving chemotherapy [21]. The Hungarian National Trophoblastic Centre also has reported a high rate of hysterectomy. In treating 335 women with GTN 14.6% underwent hysterectomy including 28.9% of women with high-risk disease. The indications for hysterectomy included management at presentation, complications such as vaginal bleeding and resection of chemo-resistant disease [22].

In summary the use of hysterectomy is highly variable and probably reflects disease presentation, local management policies and healthcare resources.

21.4.2 Use of hysterectomy in the management of the complications of treatment for gestational trophoblastic neoplasia

Hysterectomy has an important role to play in the management of the complications of treatment for gestational trophoblastic neoplasia. The two commonest indications for its use being:

- control of excessive vaginal bleeding following the onset of chemotherapy.
- management of chemo-resistant GTN which is localised to the uterus.

GTN is highly vascular and it is believed that with the death of the trophoblastic cells, there is little tissue support for the vascular tissue associated with these tumours. Vaginal bleeding at the start of chemotherapy is a common event and although excessive bleeding is rare it may still require hysterectomy. The Philippine General Hospital reported that of the 116 women who underwent hysterectomy the indication was for uterine perforation in 24% of cases and vaginal bleeding in 10% [20]. In Sheffield four patients, 6.5% of the hysterectomy group, required emergency hysterectomy following commencement of chemotherapy, three patients developed life threatening vaginal bleeding and one needed emergency surgery for abdominal pain from intra-abdominal bleeding [18].

Hysterectomy may be considered in the management of chemo-resistant gestational trophoblastic disease.

Figure 21.2 Uterus showing large deposit of resistant CC.



The number of women who undergo hysterectomy in this situation will be dependent on the case-mix of patients being treated and the advantages and disadvantages of hysterectomy when compared to the use of second or third line chemotherapy. Women who have chemo-resistant disease localised to the uterus are likely to benefit from hysterectomy whereas women who initially present with metastatic disease may not respond because of the presence of occult metastatic disease at the time of surgery.

Many centres have published their experience of hysterectomy in the management of GTN. The Charing Cross Hospital group, when reviewing their earlier experience described a rate of 8.8% in women undergoing salvage hysterectomy following chemotherapy for high-risk GTN [23]. Of the 13 women who underwent hysterectomy in this group, only two were deemed to have demonstrated a major benefit from surgery. Only 4 of the women who underwent hysterectomy showed any histological evidence of residual GTN. A more recent review by the Charing Cross reported that 0.2% or 11 of 213 registered cases of GTN underwent hysterectomy for resistant disease which included 4 cases of placental site trophoblastic tumour. In keeping with the high risk nature of this group 21 women required further chemotherapy and the mortality rate was 12% [24].

In Sheffield between 1986 and 2007, 627 (7.1%) patients were treated with chemotherapy out of 8860 new patients registered with the Centre. Sixty two of these patients underwent hysterectomy as part of their management for GTN, an incidence of 9.9%. 22 women underwent hysterectomy for chemo-resistant disease with 6 (27%) requiring further chemotherapy. The overall remission rate was 87% with a high preoperative GTN risk score being the most significant variable in predicting postoperative morbidity and mortality [18].

Lurain et al in their review of the management of high risk GTN at the Brewer Center reported complete remission in fifteen (88%) out of 17 patients who underwent hysterectomy; 14 had hysterectomy for chemo-resistant disease whilst it was adjuvant to chemotherapy in the other 3 patients [25]. Suzuka et al studied the role of adjuvant hysterectomy in the management of low risk GTN. 37(32%) patients in their review underwent planned hysterectomy two weeks after the initial course of chemotherapy and 36 (97.3%) had full remission [26].

The New England Trophoblastic Disease Centre reviewed the indications for hysterectomy between 1959 and 2009. Indications included the initial management at presentation, drug resistant disease and haemorrhage. The rate of hysterectomy was stable over the time period but there was a significant fall in the number of women undergoing hysterectomy for the management of haemorrhage (29% vs 8%) [27].

Hysterectomy therefore has an important but limited role in the management of chemo-resistant GTN and when used appropriately can reduce the need for further chemotherapy.

21.4.3 Surgical Considerations

Hysterectomy undertaken for gestational trophoblastic disease can be a challenging procedure [24,28]. Concern over the possibility of embolisation of tumour at the time of the surgical manipulation has been expressed and some centres use prophylactic chemotherapy at the time of hysterectomy. The policy at the Sheffield Centre is not to use chemotherapy. Given the rarity of the condition and the procedure it would be very difficult to assess if there was any advantage to the routine prophylactic use of chemotherapy at the time of surgery. An extensive vascular supply to the uterus and the presence of extra-uterine disease, unrecognised by imaging prior to surgery, make for difficult surgery. The necrotic nature of the tumour makes it difficult to obtain haemostasis and protracted bleeding can ensue. Excessive uterine manipulation should be avoided when possible so as to reduce any possible risk of embolisation of trophoblastic tissue. Because these patients may be haemodynamically unstable it is recommended that these procedures should be carried out by an experienced surgical team at a specialised centre providing full medical support, including

intensive care.

In the series from Sheffield significant complications related to surgery were reported in six cases; three had post-operative wound infection warranting admission to hospital, two developed disseminated intravascular coagulopathy (DIC) due to excessive bleeding at the time of surgery and one patient underwent re-implantation of the ureter into the bladder as part of the management of parametrial spread of the disease. There were no peri-operative deaths [18].

21.5 CONSERVATIVE PROCEDURES IN THE MANAGEMENT OF UTERINE BLEEDING

21.5.1 Avoiding uterine surgery

Conservative approaches to persistent vaginal bleeding should be considered in women who are desirous of future fertility and keen to avoid hysterectomy. In patients who are haemodynamically stable this option should also be considered. Selective embolisation of the major pelvic blood supply to tumour can be performed by interventional radiology. The use of polyvinyl alcohol particles or gel/foam pellets has been described with good effect [29]. Embolisation of the vessels may not stop uterine bleeding completely given that there is often an extensive blood supply feeding the uterus and therefore the tumour bed. Embolisation is more likely to result in a significant reduction in uterine bleeding which the patient can tolerate. The Charing Cross group have reported the use of arterial embolisation in a series of 14 cases [30]. Haemorrhage was controlled in 11 cases, two patients required hysterectomy and one patient underwent ligation of the uterine artery for persistent haemorrhage. Six women required repeat embolisation for a recurrence of the bleeding. Indicators of a successful outcome included the ability to selectively embolise the uterine artery and a greater than 80% reduction in vascular malformation size. A total of five pregnancies have been achieved by this group of women, including three full term infants. In a review of another 19 cases, between 2000-9, nine underwent emergency embolisation and 10 elective embolisation. Four required a second embolisation and one woman underwent hysterectomy because of bleeding despite a second attempt at embolisation. The women who underwent elective embolisation represent a small group who develop a persistent arterio-venous malformation following successful treatment of GTN. Lower abdominal pain was the most common side effect of embolisation with about 50% requiring opiates to control the pain. Fertility after embolisation in this group was high with nine having successful pregnancies, two had miscarriages and there was one ectopic pregnancy. [31]

Selective ligation of the internal iliac artery has been

recommended in the management of severe post partum haemorrhage. This technique should be considered in patients with heavy bleeding with persistent GTD or post molar vascular malformation [32] and there are case reports where this has been successful. Unfortunately few gynaecologists are experienced at this technique and, if it is to be undertaken, liaison with vascular surgery colleagues is recommended.

21.5.2 Conservative uterine surgery

There have been several published reports describing localised excision of disease within the uterus [33]. In all cases the decision for conservative uterine surgery was based on the desire for future fertility. While this appears to be a successful approach, chemotherapy is still required for successful management of these patients. It is unclear whether these patients may have benefited from chemotherapy alone without the need for subsequent surgery.

21.6 SURGERY FOR METASTATIC DISEASE

Excessive intra-lesional bleeding may also occur at sites of metastatic disease including the thorax, pelvis and brain. Bleeding within cerebral metastasis can be catastrophic and it is recommended that brain metastases should be treated with surgery or radiotherapy at, or prior to, the start of systemic chemotherapy. Surgery has been used in the management of metastatic disease. Localised metastatic disease in the lung can benefit from surgical resection with either lobectomy or partial thoracotomy.

Figure 18.3 Lung showing isolated metastatic deposit

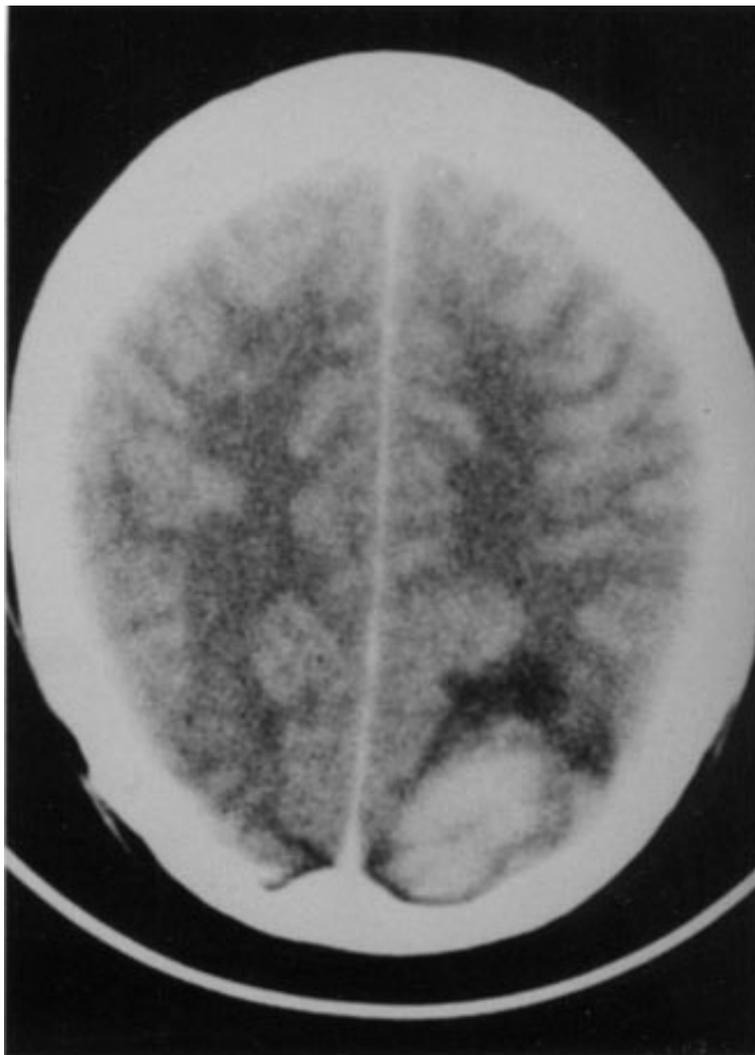


Several series have reported remission rates in the region of 66% -

85% [34,35]. Metastatic disease affecting the large and small bowel may result in patients presenting with acute obstruction and perforation. Management will be determined as for the complications associated with obstruction or perforation. In a review of surgery for high risk GTN Lurain et al reported 11 cases where pulmonary resection was performed for resistant foci. In addition one patient underwent small bowel resection because of haemorrhage from a metastasis [25, 36].

Partial hepatectomies have been performed in the management of persistent GTN. In our experience unfortunately this has failed to make a significant impact on the outcome of the disease. Metastasis to the CNS also occurs with GTN. The blood/brain barrier may prevent penetration of chemotherapeutic agents and so surgery or radiotherapy to these metastases has been considered [37]. Emergency surgery may be indicated to prevent cerebral haemorrhage or relieve increasing intracranial pressure.

Figure 21.4 CT scan showing brain metastasis of choriocarcinoma later removed surgically.



Metastatic GTN can often present as vaginal nodules, which may be

in part responsible for presentation of heavy vaginal bleeding. These nodules are very vascular and therefore respond to chemotherapy. Biopsy of these nodules can be hazardous leading to excessive vaginal bleeding which may be difficult to control and so should be avoided unless absolutely necessary.

The Hungarian National Trophoblastic Centre reported that 3.8% of women with low risk GTN underwent surgery for metastatic disease compared with 19% with high risk GTN. The most common site for resection of disease was the vagina followed by the pelvic adnexae, lung, omentum and kidney [22]. Surgery to foci of chemo-resistant metastatic disease is therefore both feasible and curative.

21.7 PLACENTAL SITE TROPHOBLASTIC TUMOUR

This is a rare form of GTN, which was first described in 1976. Patients present with symptoms and signs similar to other GTN but often have low hCG levels when compared with other GTN. These tumours are said to be less responsive to chemotherapy and if this is indicated patients should receive multi-agent regimens.

Several investigators have reported that the majority of patients are cured with hysterectomy alone when the tumour confined to uterus [38-40]. In Sheffield we have performed hysterectomy in nine cases of PSTT and three dimorphic tumours demonstrating features of PSTT. In five cases the diagnosis of PSTT was known prior to hysterectomy and only one patient, who had co-existing vaginal metastases, required chemotherapy and all are alive and well. In the seven other cases four patients required post-operative chemotherapy and two died of their disease. The cure rate in cases where their preoperative assessment confirmed only uterine disease was 100%. Several authors have reported the use of conservative surgery for PSTT confined to the uterus that has been curative and with subsequent confirmed fertility. There appears to be some difficulty in determining the extent of the disease at the time of surgery leading to high rates of positive margins [41]. However if there is evidence of extensive disease on MRI or the margins of the conservatively resected disease are positive then hysterectomy should be performed [42]. Therefore, hysterectomy is recommended in the primary management of PSTT unless there are widespread metastases [40,43]. There is little evidence that routine systematic pelvic lymphadenectomy is required in cases of PSTT; the incidence of lymph node involvement is very low and the side effects of systematic pelvis and para-aortic node dissection, e.g. lymphoedema, must be taken into account [41,44]. Involvement of retro-peritoneal lymph nodes may be associated with a long interval between the last pregnancy and clinical presentation. Current evidence suggests that lymphadenectomy should be considered in women when pre-operative imaging suggests lymphadenopathy.

21.8 SUMMARY

Surgery has an important role in the management of GTD. Molar pregnancies should be evacuated by suction curettage and medical methods of evacuation avoided. Hysterectomy may be considered as part of primary management if other gynaecological morbidity is present. In women with excessive vaginal bleeding arterial embolisation should be considered if maintenance of fertility is desirable. Hysterectomy may be required for the management of excessive uterine bleeding either at presentation or after starting chemotherapy and in the management of chemo-resistant disease localised to the pelvis. Hysterectomy is the treatment of choice of the management of placental site tumours confined to the uterus.

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