The Role of Computed Tomography Scanning of the Thorax in the Initial Assessment of Gestational Trophoblastic Neoplasia

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Objective: The aim of this study was to determine whether lesions found on computed tomography (CT) imaging of the thorax would affect FIGO (International Federation of Gynecology and Obstetrics) 2000 risk score and/or alter clinical management.

Methods: The Sheffield Trophoblastic Disease database was searched for all new patients registered for staging/scoring investigations between January 1, 2006, and June 30, 2010. The FIGO 2000 score was noted and then recalculated using information from CT scan reports. Where a change of risk score would have affected a patient's management, the case notes were further reviewed.

Results: 191 patients had undergone both modalities of imaging. Using standard FIGO scoring, 169 and 22 patients were noted to be at low and high risk, respectively. Using information from CT imaging, only a further 20 patients would have been reclassified as high risk. Fifteen of these "new" high-risk patients required salvage treatment with intravenous chemotherapy; all were cured.

Conclusions: With no potential advantage in terms of patient outcome and significantly increased radiation dose, there is little justification for routine CT imaging of the thorax in the initial assessment of new patients with gestational trophoblastic neoplasia.

Key Words: Choriocarcinoma, Gestational trophoblastic disease, Gestational trophoblastic neoplasia

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Gestational trophoblastic neoplasia (GTN) encompasses persistent/invasive mole, choriocarcinoma, and the rarer tumors, such as placental site trophoblastic tumor (PSTT). It is recognized that GTN can metastasize widely, most commonly to the lungs but also to the liver and central nervous system.[1] Overall, treatment outcomes are excellent, with cure probable even in the majority of those with metastatic disease, more than half of whom go on to achieve normal pregnancies.

Patients with GTN are classified as being at low or high risk of developing resistance to single-agent therapy using the International Federation of Gynecology and Obstetrics (FIGO) 2000 prognostic scoring system[2] (Fig. 1), which uses information from the patient's history, blood markers, and investigations. During this study, low-risk patients at our institution received intramuscularly administered (IM) methotrexate (MTX) with folinic acid, whereas those with high-risk

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Score	0	1	2	4
Age	≤ 39	> 39		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	
Months from index pregnancy	< 4	4 - 6	7 - 12	> 12
Pretreatment hCG (iu/ml)	$<10^3$	10^3 - 10^4	10^4 - 10^5	> 10^5
Largest tumour size	< 3cm	3 - 4 cm	≥ 5cm	
Site of metastases		Spleen Kidney	GI tract	Liver Brain
Number of metastases	0	1 - 4	5 - 8	> 8
Previous failed chemo			Single drug	2 or more drugs

FIGURE 1. The FIGO 2000 scoring system.

disease commenced a regimen of intravenously administered MEA (MTX alternating with dactinomycin/etoposide).[3,4] Sixty percent of low-risk patients achieved complete response to MTX.[5]

Previously, patients with GTN attending Sheffield centre underwent screening investigations including chest radiography (CXR), ultrasound scan of the pelvis, and computed tomography (CT) imaging of both the brain and thorax and lumbar puncture. Since 2009, imaging of the head has been performed only on those with clinical signs suggestive of central nervous system disease, significant lung involvement, or very high-risk disease and by magnetic resonance imaging scan alone.[6]

In 2000 at Sheffield centre, Nevin and colleagues[7] suggested that the presence of lung metastases detected on chest CT had independent statistically significant prognostic predictive power. In a follow-up study from the same center, published in 2009, Darby et al[8] concluded that CT scan of the chest used instead of CXR in the staging of GTN does not alter outcome, although low-risk patients were significantly more likely to need to change to second-line chemotherapy. Kohorn,[9] summarizing the role of imaging practices, concluded that to diagnose lung metastases and assess the FIGO risk factor score CXR is mandated. However, CT scanning may show lung micrometastases indicative of possible chemotherapy resistance. He advocated the need for prospective validatory studies. Computed tomography continued in Sheffield until 2010 to allow further, prospective evaluation of the relevance of chest CT scan to clinical practice and patient outcome, although the information gained was not used to calculate the FIGO 2000 score (which relies only on CXR).[10]

METHODS

Patients registered at Sheffield Centre over a 4½-year period between January 1, 2006, and June 30, 2010, were identified. No further ethical approval was sought for this study because all patients had already agreed to their clinical information being held on the local databases. Patients with PSTT and those in whom a diagnosis of GTN was not confirmed were excluded. The absence of either CXR or CT thorax imaging for comparison also mandated exclusion. FIGO 2000 prognostic scores that had been calculated prior to treatment decisions being made were noted. Lung involvement per se does not score, rather the size and number of lesions (Fig. 1). The FIGO risk score uses only CXR, not CT thorax, findings. These scores were then recalculated using information gathered from CT thorax scans, which were also re-reported where the original report did not indicate the size and number of metastases. Single lesions of 4 mm or less were not regarded as a metastasis. If there were multiple small lesions, they were assumed to be metastases. Other features assumed to be due to metastatic disease were solid lesions, shape (round), relationship to an adjacent vessel (ie, in proximity to or end of a vessel), margins (well defined), and association with surrounding ground-glass change (ie, hemorrhage). If a lesion was calcified*, spiculated*, related to an

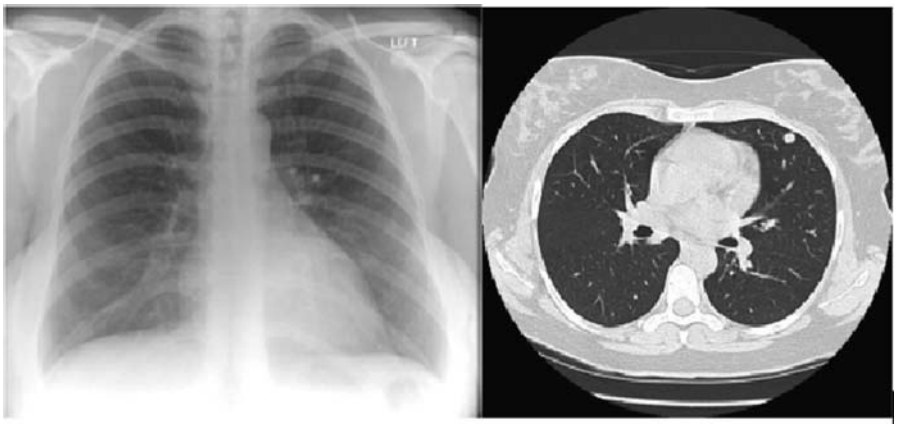

FIGURE 2. A clinical example with the CXR (reported as normal) and CT (with lung metastasis) from the same patient.

airway*, associated with thickening of the interlobular septa (ie, intrapulmonary lymph node), and/or oval shaped, it was assumed to be benign (*features for a granuloma, particularly if there is pulmonary scarring). Based on their original and recalculated FIGO scores, patients were stratified into low- and high-risk groups with scores of 0 to 6 and 7 or greater, respectively. Where the inclusion of data from CT thorax scanning, rather than just the standard use of CXR findings, would have resulted in the change of risk from low to high risk, patient records were further reviewed for detailed information on treatments given and overall disease outcomes. Fisher exact test (2×2 contingency table) was used to determine the statistical significance of differences, as 2-tailed P values, between the need for first- and second-line chemotherapy when the risk group would have been changed.

RESULTS

A total of 191 patients with confirmed GTN and available CXR and CT thorax imaging were identified. This was after 20 patients failing to meet the inclusion criteria were excluded. These comprised 5 patients with PSTT, 5 patients with incomplete imaging, 4 patients who did not receive their treatment in Sheffield, 4 patients with missing records, and 2 patients with an alternative diagnosis.

FIGO scoring identified 169 low-risk and 22 high-risk patients. Computed tomography detected additional lung metastases in 65 patients. This included 53 patients in whom metastatic lung disease was "new"; that is, the corresponding CXR was reported as normal (see example, Fig. 2). The use of information gained from CT imaging reclassified 20 patients from low- to high-risk groups (Figs. 3 and 4).

Three of the 20 patients who would have become high risk on the basis of information from CT responded completely to first-line chemotherapy with MTX alone (Table 1) with a median number of cycles of 10. During the period of this study if resistance developed, second-line therapy was commenced with single-agent dactinomycin if the hCG level was less than 150 IU/L or multiagent etoposide and dactinomycin (EA) if the hCG was greater than 150 IU/L. Two patients developed an adverse reaction to MTX. Fifteen patients required second-line treatment for MTX resistance. In 6 patients, a switch to single-agent intravenously administered dactinomycin was necessary for a persistent low-level elevation (n = 4) or a rise (n = 2) in serum hCG levels. The median number of cycles was 5. Similarly, the failure of hCG levels to fall adequately (n = 3) or instead to increase (n = 3) prompted a change to intravenously administered EA in a further 6 patients, with a median number of 8 cycles. One

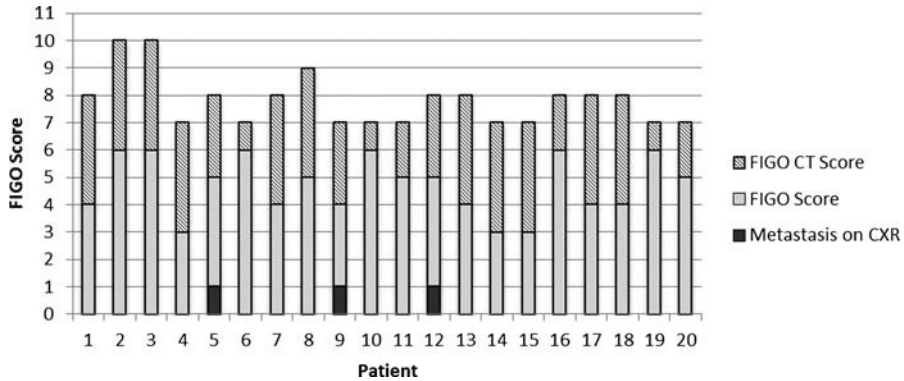

FIGURE 3. Original FIGO scores and adjusted scores with CT scan findings for the 20 patients reclassified from low to high risk.

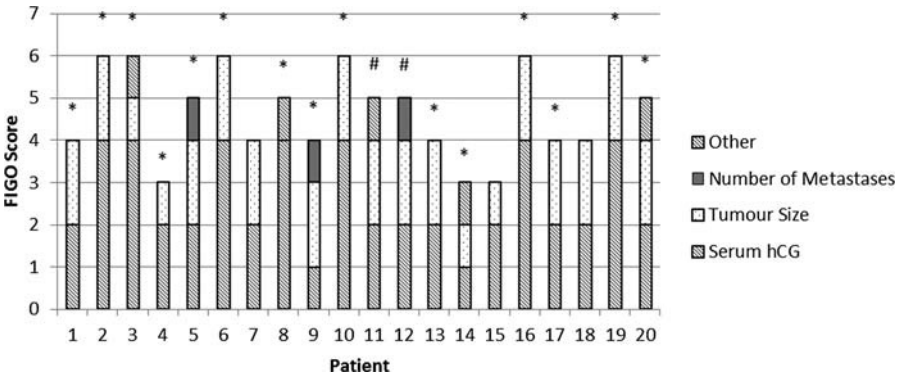

FIGURE 4. Original FIGO risk scores and composition of individual scores for the 20 patients reclassified from low to high risk. #Patients who developed toxicity from IM MTX treatment. *Patients who developed resistance to IM MTX and required second-line therapy.

patient required 1 cycle of EA and 5 cycles of intravenously administered M/EA, followed by 2 cycles of EMA. Two patients had a hysterectomy followed by third-line treatment with either EA or MTX/etoposide, dactinomycin (Fig. 5). All 20 patients are alive and well at the time of writing.

In these patients, the need to switch to second-line therapy was not dependent on the original FIGO score or on any other individual FIGO score determinant (Fig. 4). All 9 of those who scored 5/6 required a switch, but 6 of the 9 who had a score of 4 or less also needed to change ($P = 0.2$).

Thirty-two patients remained low risk despite "new" metastatic disease evident on CT imaging. Nine of these patients required second-line chemotherapy, 14 required first-line treatment only, and in the remainder (n = 9) GTN resolved spontaneously. All 32 are alive and well at the time of writing (Table 1).

Patients reclassified as high risk after CT thorax scan were more likely to require additional chemotherapy ($P = <0.001$). Those remaining at low risk were less likely to require systemic treatment ($P = <0.02$) and slightly more likely to respond to first-line MTX chemotherapy ($P = <0.07$) (Table 1).

DISCUSSION

Previous studies have sought to clarify whether CT imaging of the thorax is indicated in the initial staging/scoring of GTN. The FIGO 2000 classification uses CXR, not CT, in the assessment of lungs. In 1986, Mutch and colleagues[11] performed CT scans of the thorax in 39 patients with no known metastatic disease (as assessed by CXR) prior to treatment. Forty-one percent of patients had "new" metastatic disease on CT, and half of these required second-line chemotherapy. Computed tomography scanning was therefore suggested for routine use. In 1998, Ngan and colleagues[12] argued that small-volume lung metastases found on CT do not affect a patient's clinical outcome. Gamer and colleagues[13] in 2004 concluded that lesions on chest CT are not predictive of clinical outcome. The controversy has continued, but it has been suggested that metastatic lesions on CT may be indicative of chemotherapy resistance.[9] Previous studies from Sheffield have attempted to resolve this issue. In 2000, Nevin and colleagues[7] suggested that the presence of chest metastases on chest CT had independent statistically significant prognostic predictive power. In a follow-up study, Darby et al,[8] in 2009, concluded that CT scan of the chest used instead of CXR in the staging of GTN does not alter outcome. Our present results reiterate that lung involvement on CT imaging predicts the need to change from first-line chemotherapy. This seems to be the case irrespective of the original risk score, as 6 of 9 patients with positive CT scans who were otherwise very low risk (FIGO score of ≤4) went on to require second-line chemotherapy. In those patients who changed risk on the basis of CT thorax findings, we did not find any other individual FIGO score determinant that helped better define the need for second-line chemotherapy.

TABLE 1. Treatment given for patients with metastatic disease rescored as ''high risk'' on CT imaging

	No Systemic Treatment	1st-Line Treatment IM MTX	2nd-Line Treatment Resistant to IM MTX
Metastatic disease on CT with "new" risk score <7 (n = 32)	9/32* (28%)	14/32† (44%)	9/32‡ (28%)
Metastatic disease on CT with "new" risk score ≥7 (n = 20)	0*	3/18† (17%)	15/18‡ (83%)

*$P < 0.02$.
†$P < 0.07$.
‡$P < 0.001$.

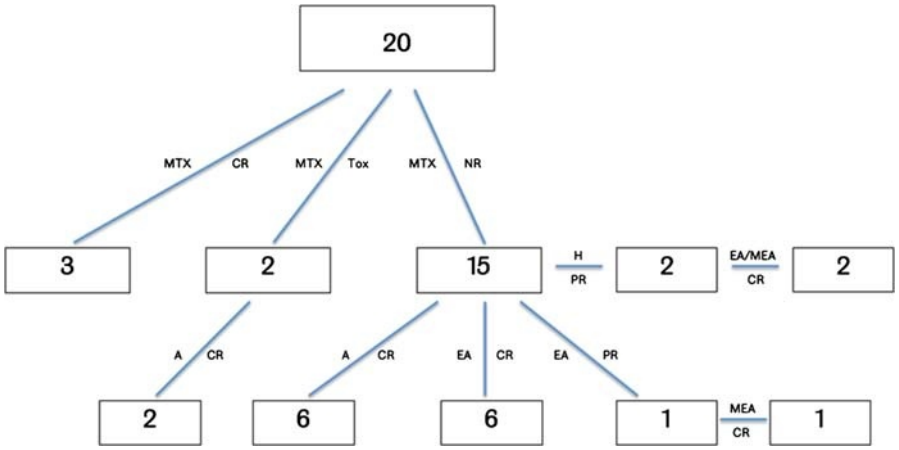

FIGURE 5. Treatments and outcomes of patients reclassified from low to high risk on the basis of CT thorax findings A indicates dactinomycin; EA, etoposide/dactinomycin; MEA, MTX, etoposide, dactinomycin; H, hysterectomy; Tox, MTX toxicity; CR, complete response; PR, partial response; NR, nonresponse.

It has been suggested that, as CT imaging technology has improved over time with more images with thinner slice thickness being acquired, smaller lesions suggestive of metastasis may in fact be benign granulomata and of no clinical significance.[14] This would lead to the overstaging of some patients, and this risk was minimized in our study by rereview of CT scan findings by an expert oncology radiologist (S.A.).

In addition to the financial cost of CT imaging, the radiation dose of CT must be considered in patients who, by definition, are of childbearing ages. The exact effective dose varies depending on the size of the patient, the machine being used, and the operator, but as a guide, a CXR has a radiation dose of 0.02 mSV, roughly equivalent to a long-haul flight, with a 1 in 1,000,000 chance of developing a fatal cancer, whereas a CT has a dose of 8 mSv, which is significantly higher and carries a 1 in 2500 chance of the same outcome.

The breast tissue in younger patients and the proliferating mammary glands during pregnancy have increased radiosensitivity.[14] Radiation dose to the breast tissue in chest CT has been estimated to be between 10 and 70 mGy.[15,16] It has also been reported that a single 10-mGy dose to women younger than 35 years increases the lifetime risk of breast cancer by 14%. Although this figure is likely to be an overestimation, it is generally accepted that radiation doses used in CT often approach or exceed those levels known to increase probability of nonfatal and fatal cancers.[15,17–19]

Using the information from CT imaging when determining the appropriate chemotherapy regimen would also mean more patients undergo high-risk chemotherapy. We have shown that not all of these patients necessarily require this, or indeed any systemic treatment, and it is acknowledged that intravenously administered MEA is a more toxic regimen than IM MTX.

The counter-argument is that a significant proportion of patients who initially undergo IM MTX do require a switch, and by treating with high-risk chemotherapy up front, such patients could spend less time overall receiving treatment, which may be beneficial for patients and clinicians alike.

From this study, albeit relatively small, it seems likely that only a small proportion (<10%) of patients would have had their first-line treatment response changed by a positive CT scan. With no potential advantage in terms of eventual outcome, there is little justification for routine CT scanning in the initial assessment of all patients with GTN. Therefore, since 2010, based on previous clinical experience, in Sheffield, CT scan is done only if there is a clinical indication, for example, positive or equivocal CXR and/or chest symptoms and signs. This policy is presently being reevaluated.

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