Computed tomography chest imaging offers no advantage over chest X-ray in the initial assessment of gestational trophoblastic neoplasia

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BACKGROUND: The International Federation of Gynaecology and Obstetrics (FIGO) score identifies gestational trophoblastic neoplasia (GTN) patients as low- or high-risk of single-agent chemotherapy resistance (SACR). Computed tomography (CT) has greater sensitivity than chest X-ray (CXR) in detecting pulmonary metastases, but effects upon outcomes remain unclear.

METHODS: Five hundred and eighty-nine patients underwent both CXR and CT during GTN assessment. Treatment decisions were CXR based. The number of metastases, risk scores, and risk category using CXR versus CT were compared. CT-derived chest assessment was evaluated as impact upon treatment decision compared to patient outcome, incidence of SACR, time-to-normal human chorionic gonadotrophin hormone (TNhCG), and primary chemotherapy resistance (PCR).

RESULTS: Metastasis detection (p < 0.0001) and FIGO score (p = 0.001) were higher using CT versus CXR. CT would have increased FIGO score in 188 (31.9%), with 43 re-classified from low- to high-risk, of whom 23 (53.5%) received curative single-agent chemotherapy. SACR was higher when score (p = 0.044) or risk group (p < 0.0001) changed. Metastases on CXR (p = 0.019) but not CT (p = 0.088) lengthened TNhCG. Logistic regression analysis found no difference between CXR (area under the curve (AUC) = 0.63) versus CT (AUC = 0.64) in predicting PCR.

CONCLUSIONS: CT chest would improve the prediction of SACR, but does not influence overall treatment outcome, TNhCG, or prediction of PCR. Lower radiation doses and cost mean ongoing CXR-based assessment is recommended.
CT-derived chest assessment was evaluated in four different ways: (i) the effect upon treatment decisions compared to actual patient outcome; (ii) observed incidence of single-agent chemotherapy resistance; (iii) the effect upon TnHCG; a surrogate marker for remission; and (iv) the prediction of primary chemotherapy resistance in all treated patients. Separate secondary analyses were performed: (1) upon groups (i)–(iii) to study patients with chest metastases detectable only on CT; and (ii) to analyse the incidence of relapse and death in the dataset. Treatment decisions were based upon CXR-derived assessment of GTN, and treatment changes indicated by CT were not carried out.

METHODS

Data collection

All patients diagnosed with GTN and referred to the Sheffield Trophoblastic Centre between January 1973 and April 2019 (n = 1294) were included in this study. Patients were excluded if they had: (i) histology inconsistent with Gestational Trophoblastic Disease following review by specialist pathologists at the Sheffield Trophoblastic Centre; (ii) were not treated (with either chemotherapy or surgery beyond the initial uterine evacuations); (iii) diagnosed with rare histological subtypes of PSTT or ET; and (iv) duplicate data entries. Included patients had: (i) undergone both a CXR and CT chest during initial investigations for GTN; (ii) a complete FIGO score, including a breakdown of the eight contributing components; and (iii) outcome data regarding single-agent and primary chemotherapy response (treatment resistance (TR) versus complete response (CR)). Single-agent chemotherapy involved patients categorised as low-risk, whereas primary chemotherapy was defined as first-line treatment in low- or high-risk patients, and as such could be single or multi-agent. TR to single-agent or primary chemotherapy was defined as a rise in ≥2 serial serum hCG levels over 4 weeks, or ≥3 consecutive hCG readings that did not fall as expected (by ~25%) over the same time period.17 Relapse was defined as ≥2 rising serial serum hCG levels in the absence of a new pregnancy or alternative explanation, following ≥6 weeks of normal serum hCG levels following the completion of chemotherapy to initially achieve CR.18 Treatment decisions were entirely based on CXR-derived assessment of GTN. Selection and details of chemotherapy regimens can be found in Supplementary Table S1.

CXR and CT chest images were reviewed and re-reported when the original report did not comment upon the exact number and size of metastases. In line with the criteria previously reported by Price et al.,9 radiographic features deemed to represent metastases included solid, well-defined lesions of a round shape in the proximity of, or at the end of, a vessel, with evidence of surrounding haemorrhage (ground-glass opacification). Multiple small lesions were assumed to be metastases, while lesions suggestive of a granuloma (calcified, spiculated, and in relation to an airway) or benign lesion (oval in shape, thickened interlobular septa) were excluded. Lesions that remained uncertain in nature were reviewed upon serial imaging, and those that did not resolve with treatment were deemed to be non-metastatic and excluded from the analysis. Lesions of all sizes that satisfied the above criteria were included and counted, to the smallest detectable size of 1 mm.

Statistical analysis

Raw data (total number of metastases, FIGO score, and TnHCG) were checked for normality (Shapiro–Wilk test) prior to statistical analysis. Wilcoxon matched-pairs signed-rank test was used to compare the total number of metastases detected on CXR versus CT. Paired nominal data in terms of FIGO risk category (low-risk versus high-risk) and response to single-agent chemotherapy (TR versus CR) were compared using McNemar’s test. Fisher’s exact test was used to compare rates of single-agent chemotherapy resistance among patients whose total FIGO score and risk category had changed as a result of CT-derived chest imaging. Differences in TnHCG were investigated using the log-rank Mantel–Cox test. Finally, binomial logistic regression analyses were used for the prediction of TR to primary chemotherapy using multiple categorical or continuous variables, with no assumption of independence between these variables. Statistical analyses were performed in GraphPad Prism (version 8, San Diego, CA, USA) and MatLab (version R2018b, Natick, MA, USA).

Results

Of the 1294 patients included, 589 met the inclusion criteria (CONSORT diagram and Supplementary Table S2). The total number of metastases detected on CT chest was significantly higher than on CXR (Wilcoxon matched-pairs signed-rank test p < 0.0001, CT interquartile range (IQR) = 3, CXR IQR = 1). Therefore, the FIGO score derived using CT was significantly higher compared to CXR (Mann–Whitney test p = 0.001) (Fig. 1 and Supplementary Fig. S1). Using CT, the FIGO score would have been different in 195 (33.1%) cases, increasing in 188 patients (96.4%) by a median of 1 point (IQR 1–3, maximum 4 points) and decreasing in 7 patients (3.6%) by a median of 1 point (IQR 1–2, maximum 2 points). This would have affected the categorisation of patients into low- or high-risk groups (McNemar’s test, p < 0.001) (Table 1), with CT reclassifying 43 (7.3%) patients from the low- to high-risk group.

Fig. 1 Box and whisker plot comparing the FIGO scores calculated using CXR- versus CT-based imaging of pulmonary metastases. The threshold line delineates a FIGO score of 7; the cut-off for categorising patients as low- versus high-risk. FIGO International Federation of Gynaecology and Obstetrics, CXR chest X-ray, CT computerised tomography (chest).

| CT | LR | HR |
|----|----|----|
| CXR | 475 | 43 |
| HR | 0 | 71 |

CXR chest X-ray, CT computerised tomography (chest), LR low-risk of single-agent chemotherapy resistance, HR high-risk of single-agent chemotherapy resistance.
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Impact upon treatment decisions and patient outcome
All treatment decisions were based on CXR alone. However, if CT had been used, of the 43 patients who would have been reclassified from the low- to high-risk group, 14 (32.6%) had CR, and 29 (67.4%) demonstrated TR to single-agent chemotherapy (Fig. 2). All received methotrexate based on their original score.

Of the 29 patients who had TR to single-agent chemotherapy, 9 were cured with second-line, single-agent chemotherapy (dactinomycin n = 8, carboplatin n = 1). Therefore, despite being changed from the low- to high-risk group, 23 (53.5%) of the 43 patients achieved a cure with first- or second-line, single-agent chemotherapy.

The remaining 20 patients with TR to single-agent chemotherapy required multi-agent second- (n = 15) or third-line (n = 5) chemotherapy or surgery (total abdominal hysterectomy) to achieve a cure (Fig. 2).

Table 2. Using CT chest, the breakdown of single-agent chemotherapy response of patients whose FIGO score changed (n = 195) versus those whose score remained unchanged (n = 394) (Fisher’s exact test p = 0.0435, n = 589).

| Response to single-agent treatment (%) of total | TR | CR |
|-----------------------------------------------|----|----|
| Score unchanged with CT                        | 126 (32.0) | 268 (68.0) |
| Score changed with CT                          | 79 (40.5)   | 116 (59.5)  |

Table 3. Using CT chest, breakdown of single-agent chemotherapy response of patients whose FIGO category changed from low- to high-risk (n = 43) versus those whose risk category remained unchanged (n = 546) (Fisher’s exact test p < 0.0001, n = 589).

| Response to single-agent treatment (%) of total | TR | CR |
|-----------------------------------------------|----|----|
| Risk category unchanged with CT               | 176 (32.2) | 370 (67.8) |
| Risk category changed with CT                 | 29 (67.4)   | 14 (32.6)   |

Observe incidence of single-agent chemotherapy resistance
The incidence of TR to single-agent chemotherapy was significantly higher among patients whose FIGO score would have changed using CT versus those whose score remained unchanged (Fisher’s exact test p = 0.0444) (Table 2). The incidence of TR to single-agent chemotherapy was also statistically higher in patients who would have changed from low- to high-risk groups, versus those whose risk did not change (Fisher’s exact test p < 0.0001) (Table 3).

Effect upon time to remission (TNhCG)
Patients with pulmonary metastases identified on CXR had a significantly longer TNhCG: median TNhCG with no metastases on CXR = 174 days versus 201 days with metastases (log-rank Mantel–Cox test p = 0.014). However, metastases on CT were not associated with a longer TNhCG: median TNhCG with no metastases on CT = 173 days versus 182 days with metastases (log-rank Mantel–Cox test p = 0.088). TNhCG did not differ between patients who would have changed risk category compared to those whose risk remained unchanged: median TNhCG 181 versus 175 days respectively (log-rank Mantel–Cox test p = 0.875).

Refer to the larger patient dataset of 1041 patients diagnosed with GTN who required treatment (chemotherapy or surgery other than uterine evacuations), simply performing a CT scan did not affect TNhCG (median TNhCG = 177 days in 640 patients who had a CT chest versus 169 days in 360 patients who did not undergo a CT chest) (log-rank Mantel–Cox test p = 0.063).
Pulmonary metastases detectable only on CT
In 145 (24.6%) patients, pulmonary metastases were detectable only on CT, which was associated with a statistically higher FIGO score compared to patients with a clear CXR (median of 5 versus 4, Mann–Whitney test p < 0.0001) or clear CT (median of 5 versus 3, Mann–Whitney test p < 0.0001). The FIGO score increased in all 145 patients by a median of 1 point, which would have led to 36 (24.8%) patients being re-classified from the low- to high-risk group. The incidence of TR to single-agent chemotherapy would have been significantly higher among patients who changed from low- to high-risk groups, compared to those whose risk remained unchanged (Fisher’s exact test p = 0.0007).

Of the 36 patients who would have changed from low- to high-risk groups, 13 (36.1%) experienced CR to single-agent chemotherapy. The remaining 23 (63.9%) patients had TR, of whom 5 were subsequently cured with second-line, single-agent chemotherapy (dacitumycin). Overall, 18 (50%) patients were cured with first- or second-line, single-agent chemotherapy. The remainder required multi-agent chemotherapy or surgery as second- (n = 14) or third-line (n = 4) management.

The incidence of TR to single-agent chemotherapy did not differ between patients with metastases detectable only on CT compared to those with a clear CT (Fisher’s exact test p = 0.119).

Patients with pulmonary metastases detectable only on CT did not have a longer TNhCG compared to those with a clear CT chest: median TNhCG 177 days versus 173 days, respectively (log-rank Mantel–Cox test p = 0.440).

Prediction of primary chemotherapy resistance
The influence of CXR versus CT-derived FIGO score on the prediction of TR to primary chemotherapy was compared using binomial logistic regression analyses. As a baseline, the capacity of the FIGO score (derived using standard CXR-based chest imaging) to predict TR to primary chemotherapy was poor, with an area under the curve (AUC) of 0.61. For a FIGO score of 7 (the cut-off score for categorising patients as low- versus high-risk), the model had a sensitivity of 0.12 and specificity of 0.88 (Fig. 3a).

Further analyses were conducted using the categorised data from the eight clinical risk factors that constitute the FIGO score.

Comparing the predictive models derived from them using either CXR- (Fig. 3b) or CT- (Fig. 3c) based chest imaging revealed a slight, but non-significant improvement to the AUC (AUC = 0.63 versus 0.64, respectively). Despite the small change to the overall AUC, the shape of the ROC curves for both datasets were superior to the baseline curve, particularly in the low false-positive/sensitivity range. This is reflected in the superior sensitivity values when matching the specificity achieved by a FIGO score of 7, with a sensitivity of 0.27 using CXR data (Fig. 3b) versus 0.31 using CT data (Fig. 3c). In summary, combining the categorised scores from the eight clinical risk factors in a logistic regression model, as opposed to using only the FIGO score allows the identification of an additional 15 (CXR-based chest assessment) or 19 patients (CT based chest assessment) who would have TR to primary chemotherapy.

Investigating the eight FIGO risk factors more closely, only two were predictive of primary chemotherapy resistance. Within both CXR and CT chest derived logistic models, the most significant factor was hCG score (p < 0.001), with antecedent pregnancy next (p < 0.05 for CT and p < 0.06 for CXR models) (Fig. 3b, c).

Incidence of relapse and death
Median follow-up from the date of evacuation was 51.7 months (IQR = 18.0–70.2 months). A total of 18 patients relapsed. The incidence of relapse was unaffected by the presence of pulmonary metastases detected on CXR (Fisher’s exact test p = 0.189, n = 589) or CT chest (Fisher’s exact test p = 0.224, n = 589) (Supplementary Table S3). Three patients died from GTN. Of these, one patient had pulmonary metastases detected on CXR, while two patients had metastases on CT chest.

DISCUSSION
The use of CT chest over CXR in the assessment of GTN is historically controversial. CT would detect more chest metastases compared to CXR; increasing the FIGO score and changing the risk category in a proportion of patients. CT would have improved the prediction of patients who were resistant to single-agent chemotherapy, but crucially would not have improved the...
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of The International Society for the Study of Trophoblastic Diseases (ISSTD) in October 2019.

AUTHOR CONTRIBUTIONS

V.L.P., B.W.H. and R.F.H. conceived and designed the study. V.L.P. and E.W. collected and assembled data. V.L.P., W.A.E.P. and R.F.H. performed the data analysis. V.L.P., M.C.W., J.E.P., J.A.T., A.A.P. and B.W.H. interpreted the data. V.L.P. wrote the manuscript, with editorial input from M.C.W., E.W., J.E.P., J.A.T., A.A.P., B.W.H. and R.F.H. All authors approved the final version of the paper.

ADDITIONAL INFORMATION

Ethics approval and consent to participate Participant consent for this study is covered within the following study ethics approval: reference 16/NE/0292, obtained from the Health Research Authority and North East Newcastle and North Tyneside 1 NHS Research Ethics Committee. The study was performed in accordance with the Declaration of Helsinki.

Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare no competing interests.

Funding information V.L.P.’s salary as a Clinical Research Fellow is funded by two large grants (CA154 and CA184) from Weston Park Cancer Charity (Sheffield, UK). The funder had no role in study design, data collection, analysis, interpretation or writing of the report.

Supplementary information is available for this paper at https://doi.org/10.1038/s41416-020-01206-8.

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