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The added value of hysterectomy in the management of gestational trophoblastic neoplasia

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HIGHLIGHTS

- Main reasons for hysterectomy were chemo-resistance, primary definitive treatment and hemorrhage.
- In localized disease, complete remission after hysterectomy was achieved in 66% of cases.
- In metastatic disease, complete remission following hysterectomy was still seen in 15.8%.
- Primary hysterectomy significantly reduced treatment duration in localized disease.

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ABSTRACT

Background. Despite the undoubted effectiveness of chemotherapeutic treatment in gestational trophoblastic neoplasia (GTN), problems related to toxicity of chemotherapy and chemo-resistant disease have led to reconsideration of the use of hysterectomy. Aim of the present study was to evaluate indications for and outcome of hysterectomy in patients with GTN in a nation-wide cohort.

Methods. Between 1977 and 2012, we identified all patients diagnosed with GTN and treated with hysterectomy from the Dutch national databases. Demographics, clinical characteristics and follow-up were recorded retrospectively.

Results. One hundred and eighteen patients (16.5% of all registered patients with GTN) underwent hysterectomy as part of their management for GTN. The majority of patients was classified as low-risk disease (74.3%), post-molar GTN (73.5%) and disease confined to the uterus (65.1%). After hysterectomy, complete remission was achieved in 66.2% of patients with localized disease and in 15.8% of patients with metastatic disease. For patients with localized disease, treated with primary hysterectomy, treatment duration was significantly shorter (mean 3.2 weeks and 8.0 weeks respectively, $p = 0.01$) with lower number of administered chemotherapy cycles (mean 1.5 and 5.8 respectively, $p < 0.01$) than patients in a matched control group.

Conclusion. In selected cases, a hysterectomy may be an effective means to either reduce or eliminate tumor bulk. Primary hysterectomy should mainly be considered in older patients with localized disease and no desire to preserve fertility, whereas patients with chemotherapy-resistant disease may benefit from additional hysterectomy, especially when disease is localized. For patients with widespread metastatic disease, the benefit of hysterectomy lies in the removal of chemotherapy-resistant tumor bulk with subsequent effect on survival.

1. Introduction

Gestational trophoblastic disease (GTD) comprises a spectrum of conditions ranging from the pre-malignant complete (CHM) and partial (PHM) hydatidiform moles to the malignant choriocarcinoma and placental site trophoblastic tumor (PSTT) [1,2]. The term gestational trophoblastic neoplasia (GTN) has been applied collectively to the malignant counterparts [3]. Post-molar GTN occurs in approximately 15–20% of complete hydatidiform moles and 0.5–1% of partial hydatidiform moles, characterized by plateauing or rising blood human chorionic gonadotrophin concentration (hCG).

The management of GTN can be considered a success story of modern medicine. Historically, hysterectomy was the treatment of choice in

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patients with GTN. In the early 1960s, outcome was poor with 5-year survival rate after hysterectomy of 41% in non-metastatic disease and 19% in metastatic disease [4]. The introduction of chemotherapy, recognition of risk factors allowing for individualized treatment and use of sensitive hCG assays as a valuable marker for monitoring disease are the main reasons for current treatment success [5]. Today, trophoblastic neoplasias are among the most curable malignancies, with cure rates approaching 90%, even in the presence of widespread disease [1,6,7].

Despite the excellent success of chemotherapy in most patients, problems related to chemo-resistant disease and toxicity have led to reconsideration of the use of hysterectomy in individualized cases. Hysterectomy with or without lymph node dissection remains the treatment of choice for PSTT, as these tumors appear fairly chemo-resistant with a propensity for lymphatic spread [8–11]. Secondary hysterectomy and metastasectomy (i.e. pulmonary resection, craniotomy, liver lobe resection) play a significant role in the management of chemo-resistant disease [1,12–14]. Response to first-line chemotherapy is estimated to be incomplete in 25% of low-risk patients and 20% of high-risk patients respectively [15]. Furthermore, surgical procedures may be inevitable in case of life-threatening hemorrhage [16,17]. A primary hysterectomy may be considered for perimenopausal patients without the desire to preserve fertility, ideally resulting in a reduction of administered cycles of chemotherapy and a subsequent reduction of toxic effects [13,17]. In addition, although the current study is mainly focused on GTN, it should be noted that hysterectomy may sometimes be considered as primary treatment for GTD [18].

Although several authors have assessed the role of hysterectomy in GTN, it generally involved small-size studies [4,12,13,17]. Apprehension of the possible benefits of hysterectomy is needed to facilitate the individual treatment decision in daily practice. In the present study, we evaluated indications for and outcome of hysterectomy in patients with GTN in a large nation-wide cohort. Considering the wide timeframe of our cohort, possible differences in indication for and outcome after hysterectomy were evaluated over time.

2. Materials and methods

2.1. Patients

Since 1977 patients with GTD are registered at the Dutch Central Registry for hydatidiform moles at the Radboud University Medical Centre, Nijmegen. This voluntary registry serves mainly as an epidemiological database and provides an hCG assay service for gynecologists nationwide. Patients with GTN are treated in referral hospitals and are discussed in the Dutch Working Party on Trophoblastic Disease. Data on patients with hysterectomy performed between 1977 and 2012 were collected from the database and records of the Dutch Working Party meetings. Moreover, hospital records of all patients were reviewed for additional information. For each patient, we reviewed demographic characteristics, FIGO 2000 prognostic scoring criteria, indication for surgery, treatment regimen, response to treatment, histological diagnosis and follow-up of at least two-years. Nine patients with PSTT were excluded from further analysis, since management and prognosis for these patients differ from other GTN patients [8–10]. One hundred and nine patients were eligible for further analysis (Fig. 1). A comparison between patients with hysterectomy performed before and after 1995 was made, to evaluate how indications for hysterectomy and outcome after hysterectomy may have changed over time. The cutoff point was chosen arbitrary, resulting in two equal timeframes.

2.2. Definitions

GTN was diagnosed according to the FIGO 2000 criteria (i.e., mola hydatidosa with serum hCG plateauing for three consecutive weeks or increasing over a period of two consecutive weeks). In line with the Dutch guidelines, the following criterion was added to this definition: at least one of the values should exceed the 95th percentile of an hCG normogram of uneventful hCG decline as constructed by Yedema et al. [19]. Chemotherapy-resistant disease was defined as a plateauing or rising serum hCG concentration in three consecutive weekly measurements. Resistance to therapy was assessed by serum hCG measurements, using an in-house developed radio-immunoassay (RIA) that detects both intact hCG and free β-subunit [20]. hCG follow-up was undertaken weekly until serum hCG was normal and then monthly until one year after completion of single-agent chemotherapy or two years after completion of multi-agent chemotherapy.

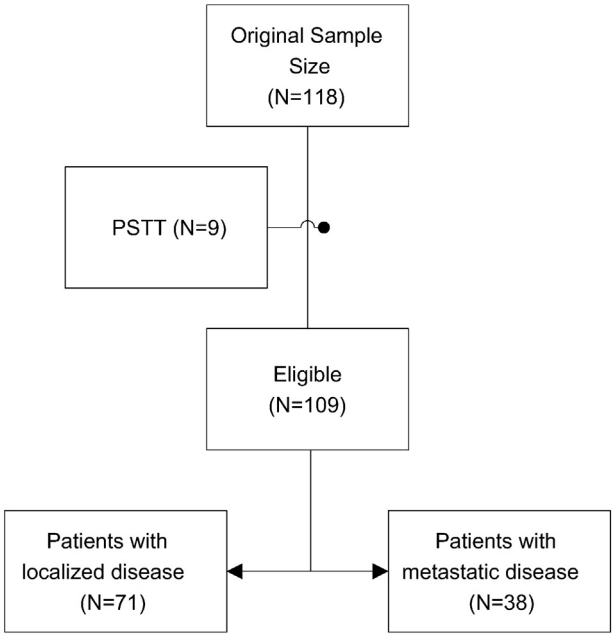

Fig. 1. Flow diagram of patient sample.

2.3. Protocols for the management of GTN

To select the appropriate treatment, all patients were classified into low- or high-risk disease using the Dutch risk classification. Risk classification with this system shows an extensive overlap with the more widely used FIGO 2000 [21]. Low-risk patients received single-agent methotrexate (MTX) with folinic acid rescue (50 mg intramuscular MTX on days 1, 3, 5, and 7 and folinic acid 15 mg orally on days 2, 4, 6, and 8). Between 1977 and 1990 high-risk patients and patients with chemo-resistant disease were treated with multi-agent chemotherapy in various effective regimens. Since 1990, the EMA/CO chemotherapeutic regimen, consisting of etoposide, methotrexate, actinomycin D alternating weekly with cyclophosphamide and vincristine is recommended as treatment of choice in patients developing resistance, unmanageable toxicity or high-risk disease [22,23].

2.4. Statistical analysis

To evaluate the therapeutic effect of hysterectomy, a comparison between patients with hysterectomy and patients without hysterectomy was performed. Due to the retrospective nature of this cohort study, patients were not randomized prior to hysterectomy. To reduce the bias of possible confounding factors, we used the propensity score matching method as described by Austin [24]. In this analysis, patients treated with hysterectomy were matched one-to-one with patients without hysterectomy treatment, based on maternal age, antecedent pregnancy, interval between evacuation and treatment, and pre-treatment serum hCG. The performance of the propensity score model was evaluated by assessing whether any important relationship between both groups and the covariates remained after adjustment. With the excellent

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