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# Efficacy of Neoadjuvant Chemotherapy for Locally Invasive Cervical Cancer During Pregnancy: An Updated Systematic Review

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**ABSTRACT**

**Background & Objective:** The management of cervical cancer during pregnancy is significantly challenging. This systematic review summarises the data on chemotherapy agents (platinum and taxanes) for the management of cervical cancer during pregnancy.

**Materials & Methods:** Two independent investigators searched the literature and extracted data from all studies that examined the efficacy and safety of platinum and taxanes in managing cervical cancer during pregnancy. A quantitative analysis of the published articles was performed and Kaplan–Meier survival curves were estimated to determine the overall and progression-free survival.

**Results:** Overall, 43 studies with 114 patients were included in this systematic review. All patients received neoadjuvant chemotherapy during pregnancy; the majority received platinum-based chemotherapy. Cisplatin was the main platinum-based chemotherapy agent in 56 patients (49%), followed by combined platinum and paclitaxel therapy in 41 patients (36%). A few patients were treated with single-agent vincristine and two patients by platinum with external beam radiation therapy. Bleomycin and 5-fluorouracil were administered to two patients. The most frequent complications were grade 2 thrombocytopenia and grade 3 hepatotoxicity in 32 (28%) and 18 (20.5%) cases, respectively. The common fetal complications were low birth weight and growth restriction. Chemotherapy was well tolerated by most women in the case group. The progression-free survival was 35% (n = 22).

**Conclusion:** Platinum and taxane neoadjuvant chemotherapy has proven to be safe and effective in preventing cervical cancer disease progression until definitive surgical treatment.

**Keywords:** Cervical Cancer, Neoadjuvant Chemotherapy, Pregnancy, Platinum, Taxanes



## 1. Introduction

The most common gynaecological cancer diagnosed during pregnancy is cervical cancer. However, its occurrence during pregnancy is rare with approximately 1 per 1,200–10,000 pregnancies **(1)**. The management of cervical cancer during pregnancy is significantly challenging; thus, it must be individualized and taken by a multidisciplinary team **(2)**. The standard treatment in nonpregnant situations includes concurrent chemoradiotherapy. There is a role of neoadjuvant chemotherapy (NACT) followed by surgery, a controversial alternative as the benefit of tumor downsizing regarding prognosis has not been proven **(3, 4)**. However, the optimal treatment for cervical cancer diagnosed during pregnancy is unclear with the absence of robust data **(5)**. Possible treatment options described in the literature include neoadjuvant platinum-based chemotherapy during the second and third trimesters, which help reduce the tumour size and optimize local control **(6)**.

The latest European Society for Medical Oncology guidelines in 2019 issued guidance on the management of cancer during pregnancy, which is also based on limited data from expert opinions and a small number of cases **(6)**. Evidence points to the benefit of platinum-based NACT during the second or third trimester of pregnancy, delaying delivery until fetal maturity

without adverse consequences for the mother and foetus **(6, 7)**. An updated systematic review and more case series are needed to provide robust evidence on the efficacy and safety of neoadjuvant platinum-based chemotherapy administration on pregnancy outcomes in women with cervical cancer. This systematic review was performed with aim to provide all the available data from the literature, evaluate the effectiveness and safety of chemotherapy agents (platinum and taxanes) in cervical cancer during pregnancy and provide recommendations for practice in local settings.

## 2. Materials and Methods

A comprehensive systematic computerised literature search was conducted on PubMed, Embase and ScienceDirect databases to identify the relevant studies published from January 2000 to September 2022 using the relevant keywords and subject terms: ((Pregnancy*) AND (cervical cancer)) AND ((neoadjuvant chemotherapy) OR (NACT)). Studies were screened based on title and abstract. Independent supplementary manual searches were conducted on the reference list of systematic review and meta-analysis articles to obtain additional eligible studies that were not acquired initially. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used as the basis of methodology **(8)**. Two independent reviewers (KKL and PSO) investigated the eligible articles and discrepancies were resolved by consensus.

Inclusion criteria were all pregnant women diagnosed with cervical cancer who were administered platinum only or combined platinum and taxanes during pregnancy. All observational studies and case series and reports were included. Exclusion criteria were all pregnant women diagnosed with cervical cancer who were not administered platinum or taxanes during pregnancy.

The selection process of relevant studies is presented in the PRISMA flow diagram. The characteristics of studies are reported in tabular format. All the investigators had separately extracted the data of included studies in the data extraction form, which contains the following relevant study information: first author, publication year, patient age at diagnosis, gestational age (GA) at diagnosis, histopathological type of cervical cancer, the International Federation of Gynaecology and Obstetrics (FIGO) stage of cervical cancer, neoadjuvant platinum-based chemotherapy regimens either platinum alone or platinum with taxanes during pregnancy, GA at the first cycle of chemotherapy administration, maternal and fetal complications, response to chemotherapy, GA at delivery, mode of delivery, fetal outcomes, neonatal weight at delivery, overall survival (OS) and progression-free survival (PFS).

The quantitative analysis of the recruited articles was divided into two parts. First, the descriptive statistics regarding the age of patients with cervical cancer, GA at delivery, GA at cervical cancer diagnosis, GA at chemotherapy administration and neonatal weight at delivery was calculated. Second, Kaplan–Meier survival curves were estimated to determine the OS and PFS of patients. Statistical analysis was performed using SPSS statistical software (version 22).

## 3. Results

### Characteristics of patients at diagnosis

The detailed characteristics of all patients are shown in Table 1. The PRISMA flow diagram reveals the initial literature search that yielded 843 published studies, of which 806 were excluded on the basis of titles and abstracts (Figure 1). After a subsequent review, a total of 43 articles were included. Among the 114 patients diagnosed with cervical cancer during pregnancy, the mean age at diagnosis was 33.3±4.2 years (ranging 24–42 years). The age of 29 patients (25.4%) was not provided. The mean GA at diagnosis was 18.9±5.2 weeks (ranging 5–36 weeks). The GA of 5 patients (<1%) was not provided. The majority of women were in second trimester (n = 100, 87.7%). Histopathological data were not available in 21 patients. Most of the histopathology includes squamous cell carcinoma (n = 73, 79%) and adenocarcinoma (n = 14, 15%). Three, one and one case had small, clear and glassy cell carcinoma of the cervix, respectively. The mean gestational age at delivery was 33 weeks (ranging 28–40 weeks). Most of the women (n = 74, 84%) were in the early FIGO stage and the remaining women were in the advanced FIGO stages IIB, III and IV (Table 1).

**Table 1. Variables extracted from literature.**

| | | Age (median) | Gestational age (median) | Gestational age at delivery (median) | Tumour size (median) | Tumour size post-chemotherapy (median) |
|---|---|---|---|---|---|---|
| N | Valid | 85 | 109 | 88 | 52 | 22 |
| | Missing | 24 | 0 | 21 | 57 | 87 |
| Mean | | 33.3294 | 18.9450 | 33.2955 | 43.8846 | 27.2455 |
| Median | | 34.0000 | 19.0000 | 33.0000 | 42.0000 | 24.0000 |

| | Age (median) | Gestational age (median) | Gestational age at delivery (median) | Tumour size (median) | Tumour size post-chemotherapy (median) |
|---|---|---|---|---|---|
| **Standard deviation** | 4.43575 | 5.22429 | 1.90075 | 17.40031 | 19.90398 |
| **Skewness** | −0.351 | 0.295 | 0.242 | 0.770 | 0.806 |
| **Standard error of skewness** | 0.261 | 0.231 | 0.257 | 0.330 | 0.491 |
| **Kurtosis** | −0.712 | 0.421 | 1.753 | 1.055 | 0.434 |
| **Standard error of kurtosis** | 0.517 | 0.459 | 0.508 | 0.650 | 0.953 |
| **Minimum** | 24.00 | 5.00 | 28.00 | 10.00 | 0.00 |
| **Maximum** | 42.00 | 36.00 | 40.00 | 94.00 | 78.00 |

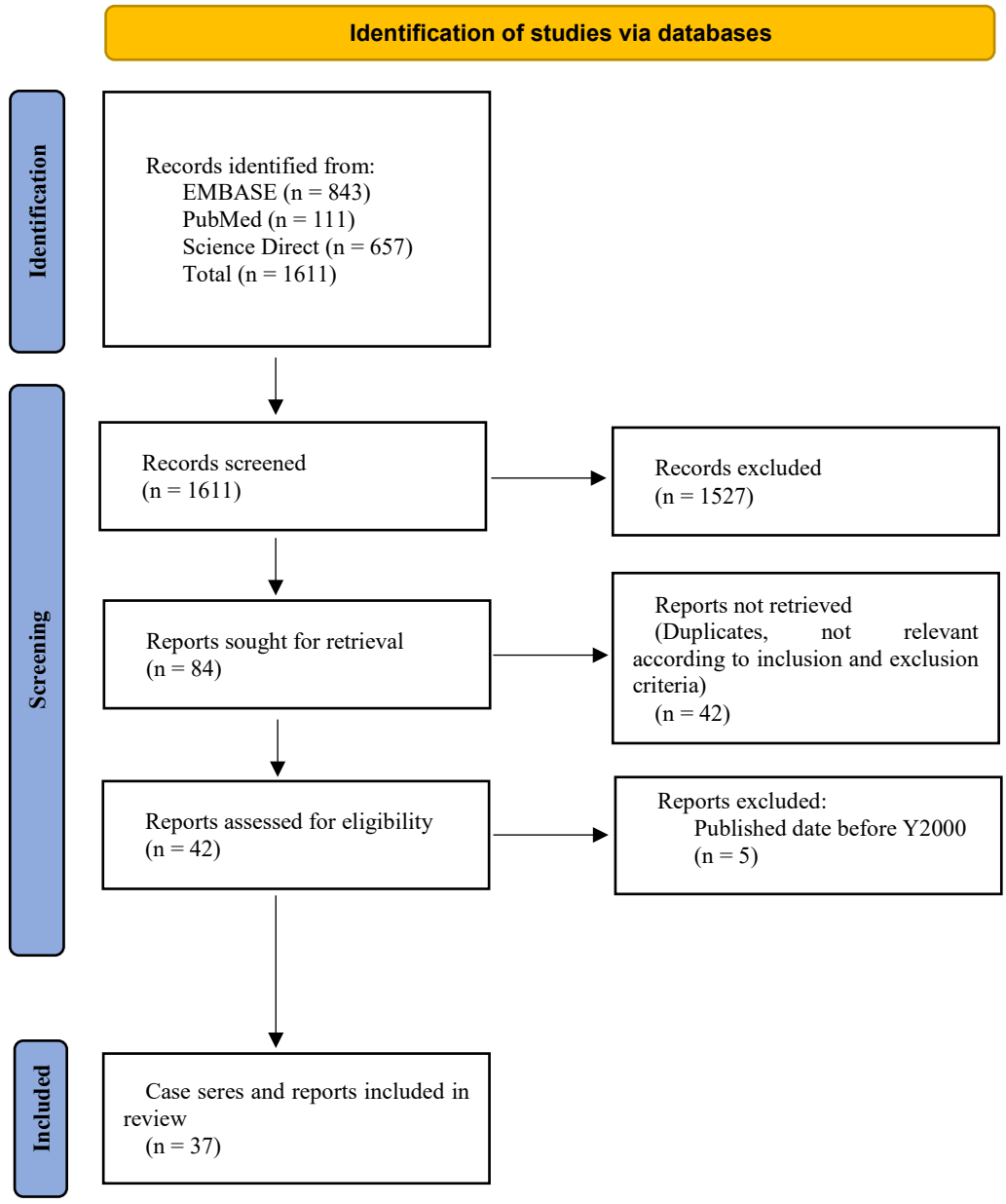


**Figure 1. PRISMA flow diagram of study selection**

### Management during pregnancy

All patients received NACT during pregnancy. Most patients received platinum-based chemotherapy. Cisplatin was the main platinum-based chemotherapy agent in 49% (n = 56) of patients, followed by combined platinum and paclitaxel therapy in 41 patients (36%). A few and two patients were treated with single-agent vincristine and platinum with external beam radiation therapy, respectively. Bleomycin and 5-fluorouracil were administered to two patients. Chemotherapy response was observed in 82 patients (72%), with partial and complete response observed in 56% and 6% of patients, respectively. Stable disease and disease progression were observed among 4% and 5% of patients, respectively. The average transverse diameter of the tumour pre- and post-chemotherapy was 43 and 27.2 mm, respectively. Out of 114 patients, 85.9% underwent a radical hysterectomy. Two patients had miscarriages and data were unavailable for other patients. Most patients (97%) underwent radical hysterectomy with pelvic lymphadenectomy. Moreover, 44% of patients underwent radiotherapy and chemotherapy as adjuvant therapy post-operatively. Approximately, 8 patients (0.7%) had recurrence within 12 months. These patients were followed up after 31.5 months.

### Safety of NACT

NACT was well tolerated by almost all patients, with mild bone marrow toxicity. Approximately, 22 cases (25.8%) required paclitaxel dosage reduction. The most frequent complications were grade 2 thrombocytopenia and grade 3 hepatotoxicity in 32 (28%) and 18 (20.5%) cases, respectively. Severe allergy was documented in six paclitaxel-related cases. Most of these side effects occurred during the second cycle of chemotherapy. Other side effects included drug intolerance, nausea, vomiting and neutropenia. One study documented the association between fetal growth restriction and low birth weight in 50% of patients. Two direct malformations were described following monotherapy with cisplatin. However, a causative link was not demonstrated. One neonatal death was described with dual therapy, which included 5-fluouracil. Severe hearing loss was documented with cisplatin and paclitaxel. After a mean follow-up of 37.6 months, all children were alive. Out of the data of 76 babies, 6% were diagnosed with respiratory distress syndrome. A further follow-up of the babies revealed one acute myeloid leukaemia and hypospadias at 22 months, one ichthyosiform erythroderma due to heterozygous *de novo* mutation in the *GJB2* gene at birth and one case of bilateral hearing loss at 6 months.

### Survival analysis

Survival analysis was performed to evaluate the OS of patients following NACT. Kaplan–Meier survival curves were depicted in Figure 2. Approximately, 52 women were alive at the end of follow-up months. The mean follow-up period was 37.6 months among 56 women for whom follow-up data were available. The PFS was 35% at follow-up. The median survival rate as depicted from the Kaplan–Meier survival curve was 59% at 63 months.

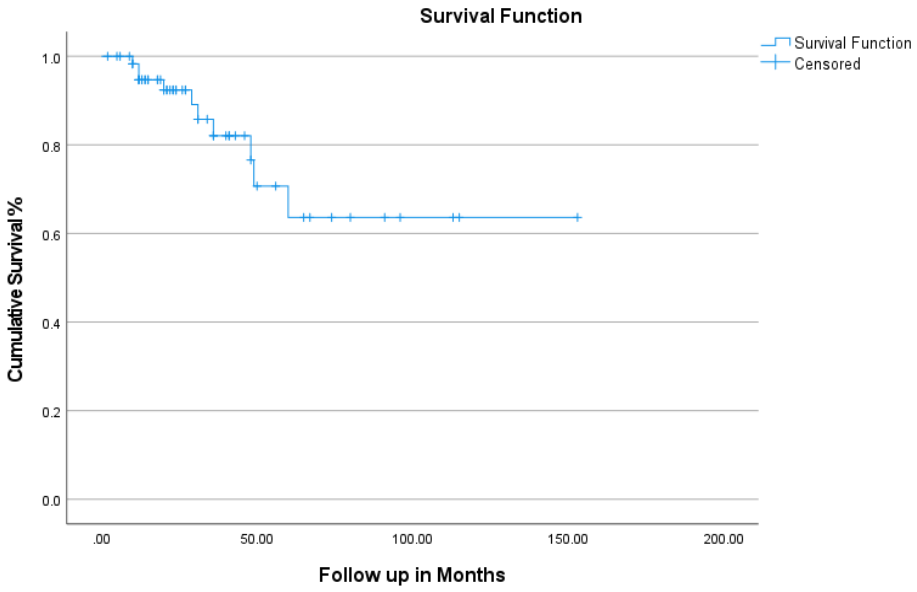


**Figure 2. Kaplan-Meir Overall Survival Curve**

## 4. Discussion

Cervical cancer during pregnancy is considered a rare event. The guidelines for managing cervical cancer during pregnancy are sparse and most of the approaches are based on expert opinions on data from a few cases (9). Hence, further studies, including case series and updated systematic reviews providing

evidence for the management of pregnant women with cervical cancer, are warranted. In this systematic review, the mean age of patients at diagnosis of cervical cancer was 32.5 years with the majority diagnosed in the early second trimester. It is important to consider the cervical cancer stage when treating it during pregnancy. The International Gynecologic Cancer Society and European Society of Gynaecological Oncology guidelines recommend a less radical surgery, such as deep cone and simple trachelectomy, for early cervical cancer with tumour size smaller than 2 cm **(10, 11)**.

The recommendations in the management for patients diagnosed after 22 weeks gestation included starting NACT or initiating optional post-partum treatment. However, for tumours stage IIA and above, NACT is the only management option of cervical cancer with continuation of pregnancy **(12)**. Approximately, 84% of women in this review had early-stage IIA cervical cancer and NACT were given and pregnancy continued. It has been proven with recent evidence that NACT is currently the innovative treatment method of choice for cervical cancer in pregnant women **(13)**. The role of NACT is to prevent the progression of cervical cancer and facilitate delayed delivery until the foetus is matured. The recommended regime is platinum-based chemotherapy **(14, 15)**. Cisplatin is the main platinum-based chemotherapy agent in 49% of patients in the present study and combination therapy with paclitaxel is the main chemotherapy of choice in 36% of patients. There are concerns about the teratogenicity of the NACT drugs. The placental transfer depends on the exposure time and dose of NACT. Few studies have documented lower concentrations of chemotherapeutic drugs in the maternal blood, amniotic fluid and umbilical cord blood when chemotherapy is performed in the second and third trimesters of pregnancy **(7)**.

The current study highlighted low birth weight and growth restriction as common fetal complications. Fetal malformation with 5-fluouracil was documented in one study. There was no direct extrapolation and congenital malformation with platinum drugs. Our review reports the follow-up of 76 babies who are alive and healthy. Respiratory distress syndrome was reported among 6.5% of neonates in the present study. A systematic review reported fetal risk of embryonal rhabdomyosarcoma following exposure to paclitaxel and one severe bilateral hearing loss at 6 months after delivery following cisplatin administration **(16)**. There was one report of acute myeloid leukaemia and the child is currently disease free **(17)**. Our review further validates the aforementioned findings. Overall, the incidence of complications of NACT is low and NACT is a relatively safe method for patients with cervical cancer to allow pregnancy continuation **(15, 18)**.

Regarding maternal complications, our review highlighted moderate toxicity such as bone marrow depression, hepatotoxicity and thrombocytopenia. A study by Song et al **(17)** further described haematologic toxicity, drug intolerance, allergic reaction, nausea and vomiting. However, chemotherapy was well tolerated in the majority of women during pregnancy **(17)**. Most of the studies reported cisplatin as widely used either alone or in combination with another drug. There is increasing evidence of the safety of carboplatin and the use of taxanes during pregnancy **(9)**.

This systematic review demonstrated the OS rate of 83.9% over a mean follow-up duration of 30.8 months. The median survival rate as depicted from the Kaplan–Meier survival curve was 59% at 63 months. Surgery is the mainstay treatment following NACT in pregnancy. Moreover, surgery has a decisive role during the time of delivery. Radical hysterectomy first described by Brunschwig in 1958 has been the treatment of choice for cervical cancer **(9, 19)**. The combination of caesarean section with radical hysterectomy increases the complexity of the procedure related to the gravid uterus, limiting access to the surgical field **(20, 21)**. Approximately, 96.4% of patients in the review underwent radical hysterectomy. Evidence from case series suggests higher incidence rates of blood loss, intraoperative haemorrhage and the need for blood transfusions **(20)**. Overall, the rate of other operative and post-operative complications is comparable with that of non-pregnant women who underwent radical hysterectomy during caesarean section **(21)**.

This review adds to the existing literature that the treatment of cervical cancer during pregnancy by NACT and radical hysterectomy is associated with good oncologic, obstetric and paediatric outcomes. Tumour response has been satisfactory, with the end point being control of the neoplastic disease until fetal viability. There is increasing evidence that the addition of taxanes may represent an option for patients diagnosed with cervical cancer during pregnancy. Accordingly, data on administering taxane in combination with platinum derivatives suggest its safety during pregnancy **(16)**.

This study has potential limitations. Included studies were case reports and case series that have the potential to be low-quality evidence. However, the total number of cases recruited with evidence contributing to existing literature in the management of cervical cancer during pregnancy increased in this study. Many individual studies did not provide the patients' follow-up data to determine the overall PFS. As many studies have a retrospective design, there can be influence the descriptive statistics or survival analyses as performed in this systematic review.

## 5. Conclusion

The results of this systematic review adds to the existing evidence on the feasibility of a systematic treatment approach for pregnant women diagnosed with cervical cancer. Neoadjuvant platinum and taxane

chemotherapy are safe and effective in preventing disease progression until definitive surgical treatment. However, further studies are warranted to support this evidence, as well as data on long-term maternal and neonatal follow-ups.

## 6. Declarations


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### Ethical Considerations

This study was approved by the IMU Joint-Committee on Research and Ethics on January 20, 2022.

### Authors' Contributions

KNG, AFS and TTW conceived and designed the analysis. KKL and PSO collected the data. KNG, KKL and PSO contributed data or analysis tools. KNG performed the analysis. KNG wrote the article and KKL, PSO, AFS and TTW reviewed and revised the paper. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

### Conflict of Interest

The authors declare no conflict of interest.


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