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# Neoadjuvant Chemotherapy in Gynecologic Cancers

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## 1. Introduction

Neoadjuvant chemotherapy is introduced in many gynecologic cancers such as cervical and ovarian cancer. The aim of using neoadjuvant chemotherapy is to reduce the tumor size prior to the principle treatment, either radiation or surgery. The benefit of reducing tumor size can increase the operability and decrease the morbidity in many types of gynecologic cancers. Besides this, neoadjuvant chemotherapy might control the micro- metastatic disease to decrease the distant metastasis (Benedetti-Panici et al., 1998; Buda et al., 2005; Chua, 2010). On the other hand, in patients who did not respond to chemotherapy, however, the administration of neoadjuvant chemotherapy risks delaying the principle treatment.
In this chapter, literature pertaining to neoadjuvant chemotherapy for gynecologic cancer will be presented in five parts, categorized by types of cancers; cervical cancer, ovarian cancer, endometrial cancer, vulvar cancer, and vaginal cancer.

## 2. Cervical cancer

Cervical cancer is the third most common malignancy in women worldwide. The GLOBOCAN project estimates that there will be 530,000 new cases in 2008. The highest incidence is in Africa and Asia. In early stage, the patients may be treated with either surgery or radiation therapy depending on preferences of both patient and physician (Undurraga et al., 2010). Whereas concurrent chemoradiation is the principle treatment in the locally advanced stage, and chemotherapy is the main treatment in advanced stage.
Neoadjuvant chemotherapy has been investigated in cervical cancer with the aim of improving the treatment outcome for over 20 years. This section presents the studies about using neoadjuvant chemotherapy in cervical cancer before radiation and surgery.

### 2.1 Neoadjuvant chemotherapy before radiation therapy

The rationale of giving neoadjuvant chemotherapy before radiation therapy included reducing tumor volume and radio- sensitizing tumors by decreasing the hypoxic cell fraction in large tumors (Movva et al., 2009). However, several randomized trials of such treatment revealed no survival advantage compared with radiation therapy alone (Chiara et al., 1994; Herod et al., 2000; Lacava et al., 1997; Leborgne et al., 1997; Sundfor et al., 1996; Souhami et al., 1991; Symonds, 2000; Tattersall et al., 1992; Tattersall et al., 1995). Furthermore, the Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-Analysis Collaboration Group presented a systematic review and meta-analysis of individual

patient data (IPD) from eighteen trials with 2,074 patients. (Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration,2003). Neoadjuvant chemotherapy before radiation therapy was compared with radiation therapy alone. The result did not show any benefit in overall survival with neoadjuvant chemotherapy. However, when the analyses were re-grouped by the interval and the dose intensity of the chemotherapy, a survival benefit was apparent in patients who received weekly and biweekly cisplatin with a dose of intensity more than 25 mg/m$^2$/week (Table 1). There was 7% absolute improvement in overall 5-year survival in trials using shorter cycles of neoadjuvant chemotherapy of less than fourteen days. This advantage was also observed in disease-free, locoregional disease-free and matastasis-free survival. In addition, trials that used a dose more than 25 mg/m$^2$/week showed an improvement of about 3% in 5-year overall survival. Conversely, in trials that administered lower dose of cisplatin (less than 25 kg/m$^2$/week) demonstrated an 11% reduction in 5-year overall survival. In the meantime, intervals longer than fourteen days trials demonstrated a decrease of 8% in 5-year overall survival. A decrease was also observed in disease-free, locoregional disease-free and matastasis-free survival. The benefit from short cycle and dose intensive cisplatin-based neoadjuvant chemotherapy prior radiation therapy suggested that chemotherapy may effectively control radioresistant cellular clones and decrease the chance of surviving tumor cell regrowth.

| Trial grouping | Number of trials | Number of events/patients | HR (95%CI, P value) | Heterogeneity P value | 5-year OS (%) |
|---|---|---|---|---|---|
| Interval of chemotherapy (days) | | | | | |
| >14 | 11 | 639/1214 | 1.25(1.07-1.46), 0.005 | 0.238 | ⇓ 8 |
| ≤14 | 6 | 417/812 | 0.76(0.62-0.92), 0.005 | 0.193 | ⇑ 7 |
| Neoadjuvant cisplatin dose intensity (mg/m$^2$) | | | | | |
| <25 | 7 | 413/845 | 1.35(1.11-1.64), 0.002 | 0.746 | ⇓ 11% |
| ≥25 | 11 | 671/1229 | 0.91(0.78-1.05), 0.200 | 0.001 | ⇑ 3% |

Table 1. Overall survival (OS) by frequency of chemotherapy and cisplatin dose intensity in comparison I (Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration,2003; Gonzalez-Martin et al., 2008)

### 2.2 Neoadjuvant chemotherapy before concurrent chemoradiation

Studies on neoadjuvant chemotherapy before concurrent chemoradiation is limited. Gonzalez et al. (Duenas-Gonzalez et al., 2002) reported a phase II study that compared neoadjuvant chemotherapy followed by surgery or concurrent chemoradiation with standard concomitant chemoradiation. There were two groups, forty-one patients with cervical carcinoma in stage IB2-IIIB each, in the study. The first group was treated with neoadjuvant chemotherapy. The treatment consisted of cisplatin 100 mg/m$^2$ given on the first day and gemcitabine 1,000 mg/m$^2$ given on day 1 and 8, followed by either surgery or concomitant chemoradiation, depending on operability. The second group was treated with six weekly courses of cisplatin 40 mg/m$^2$ during standard pelvic radiation. Both groups had comparable clinicopathological characteristics. In this study, fourteen cases from the first group underwent chemoradiation after receiving neoadjuvant chemotherapy. Of these patients, thirteen patients had a clinical complete response. Nevertheless, this small number

of patients did not conclusively demonstrate a benefit from neoadjuvant chemoradiation prior to concurrent chemoradiation. Further research is required to study this approach.

### 2.3 Neoadjuvant chemotherapy before surgery

#### 2.3.1 Neoadjuvant chemotherapy before radical surgery versus radical surgery

Several studies revealed that giving neoadjuvant chemotherapy before surgery is effective in reducing tumor size, expediting micrometastasis treatment, improving operability and surgical downstaging (Hwang et al., 2001; Panici et al., 1991; Panici et al., 1991; Sardi et al., 1993). However, the randomized phase III study from the Gynecologic Oncologic Group (GOG) failed to demonstrate a survival benefit when compared to patients who received neoadjuvant chemotherapy followed by radical hysterectomy with patients who underwent surgery alone for bulky stage IB disease (Eddy et al., 2007). In addition, in a recent Cochrane database review, six randomized control trials including 1,072 cervical cancer patients comparing neoadjuvant chemotherapy plus surgery with primary surgery showed only significantly improvements in progression free survival in the neoadjuvant chemotherapy arm. In contrast, overall survival was not improved (Rydzewska et al.,2010).

Cai et al (2006) reported a randomized study of preoperative chemotherapy versus primary radical surgery for stage IB cervical cancer patients. This study was not included in the Cochrane review. In the neoadjuvant chemotherapy arm, patients were given cisplatin 75 mg/m$^2$ on day 1 plus 5- fluorouracil 24 mg/kg/day on day 1-5 every three weeks, for two courses. The number of studied patients in the neoadjuvant chemotherapy group was fifty-two cases, while the patients in primary surgery group numbered fifty-four cases. The results demonstrated a reduction in pathological risk factors and an improvement in long-term survival in patients who received neoadjuvant chemotherapy.

Another comparative study by Cho et al (2009) compared fifty-one patients who were given neoadjuvant chemotherapy before radical hysterectomy with thirty-five patients who received radical surgery alone in stage IB2-IIA bulky cervical cancer. Both groups were well balanced in age, tumor size, FIGO stage, level of squamous cell cancer antigen, histopathologic type and grade, operating time, estimated blood loss, number of lymph nodes removed and rate of complications. There was a reduction in pathologic tumor size, and there were fewer patients with deep cervical invasion in the neoadjuvant chemotherapy group, and adjuvant radiation was given more frequently in the primary surgical group. However, there was no improvement in 5-year disease free and overall survival. These findings differed slightly from a report from Kim et al (2010). The study expressed the matched - case comparison between neoadjuvant chemotherapy before surgery group and primary surgery group in stage IB1-IIA and found more definitely reduced intermediate and high risk factors in neoadjuvant chemotherapy patients in stage IIA. Although the authors reported no significant difference in progression-free survival and disease recurrence between these two studied groups in stage IB, the patients who received neoadjuvant chemotherapy before surgery showed worse overall survival than the primary surgery group in stage IIA.

The delay in standard treatment is one important issue of concern in patients receiving neoadjuvant chemotherapy. To study this problem, Chen et al (2008) conducted a randomized study in stage IB2-IIB comparing modified preoperative neoadjuvant chemotherapy, (N=72) with primary radical surgery, (N=70). The neoadjuvant chemotherapy regimen consisted of two cycles at fourteen-day intervals of cisplatin 100 mg/m$^2$ IV given on day 1, mitomicin C 4 mg/m$^2$ IM given on day 1-5 and 5 – fluorouracil 24 mg/kg/day IV given on day 1-5. A longer tumor-free survival was observed in the neoadjuvant chemotherapy group. When using Cox hazard analysis, however, this did not indicate the therapy modality as a

prognostic predictor. The authors further analyzed the survival difference between non-neoadjuvant chemotherapy responders and the patients in the primary surgery group by using Log rank tested. There was no difference in survival between these two groups. Therefore, the modified schedule of neoadjuvant chemotherapy did not adversely delay the treatment in non-neoadjuvant chemotherapy responders.

### 2.3.2 The type of neoadjuvant chemotherapy before surgery

Many phase II studies have been reported of various neoadjuvant chemotherapy types and schedules (table 2). The response rate was over 80% in the studies using combination

| Author (year) | Chemotherapy | Stage | N | outcome |
|---|---|---|---|---|
| Zanetta et al (1998) | Paclitaxel 175 mg/m² D1& cisplatin 50 mg/m² D2-3& ifosfamide 5 gm/m2 D2-3 x 3 courses q 3 weeks | IB2-IVA | 38 | Overall RR 84%,PCR 16%,PPR 18% |
| Sugiyama et al (1999) | Cisplatin 60 mg/m² day 1-3 & Irinothecan 60 mg/m² days 1, 8, 15 x 2-3 courses q 4 weeks | IB=IIIB | 23 | CR 13%,PR 65% |
| Gonzalez et al (2001) | Cisplatin 100 mg/m² & gemcitabine 1000 mg/m² D1,8 x 2 courses q 3 weeks | IB2-IIIB | 41 | Overall RR 95%,PCR 23% |
| Gonzalez et al (2003) | Carboplatin AUC=6 & paclitaxel 175 mg/m2 x 2 courses q 3 weeks | IB2-IIIB | 41 | 63% received CCRT,CR 95%,PCR=17%, PPR = 20%, 2 years OS=79% |
| Gonzalez et al (2003) | Oxaliplatin 130 mg/m² day 1& Gemcitabine 1250 mg/m² days 1, 8 x 3 q 3 weeks | IB-IIB | 10 | RR 80%, PCR 14% |
| Termrungru-anglert et al (2005) | Cisplatin 70 mg/m² & gemcitabine 1000 mg/m² D1,8 x 2 courses q 3 weeks | IB2 | 28 | Overall RR 88.9%, PCR 8.3%,3 year OS = 88.9% |
| Suprasert et al (2007) | Cisplatin 75 mg/m² x 1-2 courses q 3 weeks | IB-IIA | 42 | PR 4.7% |
| Bae et al (2008) | cisplatin 60 mg/m² D1,2 & etoposide 100 mg/m² D1 x 3 courses q 10 days | IB-IIB | 99 | PRR 69.7%,5-year OS 88.1%,5- year PFS 60.5% |
| Matsumura et al (2010) | Irinotecan 60 mg/m² D1,8,15 & cisplatin 60 mg/m² D1 or Irinotecan 60 mg/m² D1,8 & nadaplatin 80 mg/m² D1 x 1-2 courses q 4 weeks | IB2-IIB | 46 | Overall RR 80.4%,3- year PFS 86.1% |

RR = response rate
CR = complete response
PR = partial response
PCR=pathologic complete response
PPR=pathologic partial response
PRR = pathologic response rate
PFS = Progression-free survival rate
OS = overall survival rate
CCRT = Concurrent chemoradiation

Table 2. Phase II study of neoadjuvant chemotherapy followed by radical surgery

neoadjuvant chemotherapy (Duenas-Gonzalez et al., 2001; Duenas-Gonzalez et al., 2003; Duenas-Gonzalez et al., 2003; Matsumura et al., 2010; Termrungruanglert et al., 2005; Sugiyama et al., 1999; Zanetta et al., 1998) but in our study (Suprasert et al., 2007), the response rate of using single cisplatin was very low, 4.5%. The pathologic complete response was in a range of 8.3-23% (Duenas-Gonzalez et al., 2001; Duenas-Gonzalez et al., 2003; Termrungruanglert et al., 2005; Zanetta et al., 1998). Adjuvant radiation was given to patients with intermediate and/or high risk factors in most of the studies, except the study by Matsumura et al (2010). Chemotherapy was administered in patients with high risk factors by using the same regimen as given in the neoadjuvant chemotherapy setting. The authors reported the 3-year progression free survival as 86.1%.

### 2.4 Neoadjuvant chemotherapy before surgery versus standard radiation therapy

Benedetti-Panici et al. (2002) conducted an Italian multicenter randomized study comparing cisplatin-based neoadjuvant chemotherapy followed by radical surgery versus conventional radiotherapy, in locally advance squamous cell cervical cancer. Two hundreds and ten cases were assigned to the neoadjuvant chemotherapy group and 199 cases were assigned to the conventional radiotherapy group. There was an increase in 5- year overall survival rate for patients who received neoadjuvant chemotherapy. However, when analyzed by FIGO stage, the overall survival rate significantly increased only in stage IB2 to IIB. In more advanced stages, the overall survival rate was not significantly different between the two groups. The result suggested that, the more advanced the stage, the more limited the benefit achievable by neoadjuvant chemotherapy. This could be explained by considering that the large tumor volumes were associated with a large number of hypoxic cells and high proportion of cell population in resting phases. Both events reduced chemosensitivity and probability of developing resistant clones.

Another important study (Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration, 2003) was a systematic review and meta-analysis of individual patient data from twenty-one randomized trials, which included data from the above study (Benedetti-Panici et al., 2002). Two comparisons were performed in the review. The first one compared neoadjuvant chemotherapy followed by radiotherapy versus the radiotherapy alone as discussed in the previous section (2.1). The other compared neoadjuvant chemotherapy followed by surgery with or without radiation versus radical radiotherapy. Five randomized trials with a total of 872 patients were analyzed. The planned total dose of cisplatin was in a range of 100-300 mg/m$^2$ in 10-21-day cycles while the radiation dosage was similar in each trial. The results indicated a highly significant effect of neoadjuvant chemotherapy group with overall HR of 0.65 (P=0.00004), which translated into an absolute increase in 5-year overall survival rate from 50% to 64%.

### 2.5 Neoadjuvant chemotherapy and conservative surgery

Preoperative neoadjuvant chemotherapy could reduce the tumor size and may virtually sterilize micrometastases in the paracervical tissue and pelvic lymph nodes. This effect allows for a less extensive surgery of the cervix instead of radical hysterectomy in stage IB1patients who desire to preserve fertility-sparing. Maneo et al (2008) reported sixteen stage IB1 nulliparous patients treated with three courses of preoperative chemotherapy followed by cold-knife conization and pelvic lymphadenectomy. The chemotherapy regimen for squamous cell carcinoma consisted of cisplatin 75 mg/m$^2$, paclitaxel 175 mg/m$^2$ and ifosfamide 5 gm/m$^2$, for adenocarcinoma, epirubicin 80 mg/m$^2$ was applied instead of

ifosfamide. During a median follow-up of sixty-nine months, no relapse occurred. However, three patients developed carcinoma intraepithelial neoplasia (CIN) after follow- up in long term. Regarding the fertility outcome, ten pregnancies occurred in six patients. The authors concluded that this integrated treatment was feasible.

## 3. Ovarian cancer

Neoadjuvant chemotherapy was introduced as an alternative management strategy in patients with advanced ovarian cancer approximately two decades ago (Chambers et al. ,1990). Initially, the approach was used only for patients who had significant comorbidities and could not tolerate the cytoreductive surgery. Later on, neoadjuvant chemotherapy has been advocated for the treatment of the patients with multiple sites of metastases ovarian cancer (Ansquer et al., 2001; Schwartz et al., 1999). Other advantages of the neoadjuvant chemotherapy approach include a risk reduction of peri-operative morbidity and a higher rate of optimal resection than primay debulking surgery (Baekelandt, 2003; Huober et al., 2002). The optimal resection outcome is an important factor potentially augmenting survival rate.

To review the above issues, three systematic reviews were published (Bristow & Chi, 2006; Bristow et al., 2007; Kang & Nam, 2009). The first one was presented in 2007 by Bristow et al (Bristow & Chi, 2006). They performed a meta- analysis in twenty-two cohorts studied with 835 patients in stage III-IV ovarian cancer who received neoadjuvant platinum- base that were published in MEDLINE 1989-2005. About 47% of these patients received a taxane. They presented the median overall survival of 24.5 months and found that each incremental increase in pre-operative chemotherapy cycles was associated with a decrease in median survival time of 4.1 months.

In the subsequent year, they presented a second report (Bristow et al., 2007). In that systematic review, they analyzed twenty-six studies published in the English language literature encompassing a total of 1,336 patients treated with neoadjuvant chemotherapy. The common study design was retrospective analysis in twelve reports, followed by retrospective case-control in eight reports, phase I study in four reports, and phase II study in the rest. The authors reported that 10 studies showed inferior survival in patients who received neoadjuvant chemotherapy compared with primary cytoreductive surgery whereas nine studies revealed no significant difference in survival outcome between neoadjuvant chemotherapy and primary cytoreductive surgery. With the heterogenous and predominant retrospective studies in the systematic review, the authors concluded that neoadjuvant chemotherapy should be an alternative management strategy for patients who were felt to be non-optimally resectable by an experienced ovarian cancer surgical team.

The third systematic review was published by Kang et al (2009). Twenty-one studies published between January 1989 and June 2008 met the selection criteria. Due to the heterogeneity in each study, a meta-regression analysis was implemented. The authors found that patients who received neoadjuvant chemotherapy had a lower risk of suboptimal cytoreduction than the patients with primary cytoredutive surgery. Meta-regression analysis revealed that heterogeneity in year of publication, taxane use, and optimal cytoreduction rate influenced median overall survival rate. However, the between- studies variation of the number of neoadjuvant chemotherapy cycles did not influence survival. This finding disagreed with Bristow's report. The authors suggested that the contrary result was due to the difference in statistical models and the study subjects.

In recent years, Vergote et al (2010) presented the large randomized multicenter study of stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal carcinoma patients treated with neoadjuvant platinum-based chemotherapy followed by debulking surgery compared with primary debulking surgery followed by platinum-based chemotherapy. Over 300 patients were included in each arm. The results showed a similar overall survival and progression – free survival in both groups. However, the optimal resection rate was higher in the neoadjuvant chemotherapy arm. On the other hand, the postoperative adverse effects and morbidity tended to be higher after primary debulking than after received neoadjuvant chemotherapy.

With respect to elderly patients, McLean et al (2010) reported the comparative study of the ovarian cancer patients aged over 65 who received neoadjuvant chemotherapy or primary debulking surgery. They found that the overall survival rate did not differ in both treatments. The neoadjuvant group showed a trend toward higher rate of optimal debulking and less surgical complication than primary surgery group.

Although many previous reports suggested the non-inferior outcome of neoadjuvant chemotherapy setting in advanced ovarian cancer patients, the survey results from members of the Society of Gynecologic Oncologists (SGO) revealed that the majority of the respondants did not treat patients with neoadjuvant chemotherapy followed by interval debulking (Dewdney et al., 2010). The result demonstrated that further research would be required to support the role of neoadjuvant chemotherapy in advanced ovarian cancer patients.

## 4. Endometrial cancer

Most endometrial cancer patients present at an early stage and are cured with hysterectomy and surgical staging alone. The treatment with chemotherapy is predominantly in advanced – stage disease which occurs in only 10-15% of all newly diagnosed cases (Behbakht et al., 1994; Cook et al., 1999). Many studies including a recent meta-analysis demonstrated a survival benefit when a small residual volume could be achieved after cytoreductive surgery in advanced endometrial cancer (Barlin et al.,2010; Bristow et al., 2000; Chi et al., 1997; Goff et al., 1994; Memarzadeh et al., 2002; Numazaki et al., 2009). Neoadjuvant chemotherapy was of proven benefit in advanced ovarian cancer for increase optimal cytoreductive surgery. However, the role of neoadjuvant chemotherapy was still limited in advanced endometrial cancer. Vandenput et al.(2009) investigated the value of neoadjuvant chemotherapy followed by interval debulking in thirty patients with stage IVB endometrial cancer. The most common histology was serous cystadenocarcinoma. Over 80% of these patients received paclitaxel plus carboplatin. The number of cycles before interval debulking was 3-4 cycles. Six patients (13%) were inoperable due to extensive invasion. A total of 22 out of 24 patients (92%) had complete cytoreduction and 8% had optimal cytoreduction (less than 1 cm). The median progression-free survival and overall survival times were 13 and 23 months, respectively. The survival data corresponded to the previous reports which treated stage III-IV uterine papillary serous carcinoma with primary surgery followed by chemotherapy (Memarzadeh et al, 2002; Thomas et al, 2007). The authors suggested that neoadjuvant chemotherapy followed by interval cytoreductive surgery was a reasonable option for endometrial cancer with thansperitoneal spread. Nevertheless, to support this result, further research on the role of neoadjuvant chemotherapy for endometrial cancer is required.

## 5. Vulvar cancer

Vulvar cancer, an uncommon cancer, represents approximately 4% of all gynecologic cancers. The main treatment consists of vulvectomy plus bilateral groin node dissection in early stage (de Hullu et al., 2004) and more extensive surgery in locally advanced stage (Kehoe, 2006). Although this type of surgery can be curative, it is associated with high morbidity and mortality rates. Neoadjuvant chemotherapy is an alternative approach in locally advanced vulvar cancer patients. The aim of this strategy is to downstage in an effort to avoid the morbidity from such extensive surgery.

Shimizu et al (1990) published the first related case report using a combination of bleomycin, vincristine, mitomicin C and cisplatin for three cycles in an unresectable case with FIGO stage IV squamous cell carcinoma of the vulvar. The patient had a complete response with few toxic effects and successfully underwent a subsequent radical vulvectomy with bilateral groin node dissection. After surgery, the patient was given a further two courses of these chemotherapy regimen. She was still free of disease for 20 months. The next paper was presented by Benedetti-Panici et al (1993). Twenty-one patients with locally advanced squamous cell carcinoma of the vulvar received 2-3 courses of cisplatin , bleomycin and methotrexate followed by radical surgery in operable patients. Of these patients, 10% had a measurable response in the primary tumor and 67% in the groin nodes, without serious morbidity. The operability rate following neoadjuvant chemotherapy was 90% , but only 79% underwent radical surgery. On the other hand, 3- year survival rate was only 24%; 68% of the operated patients recurred 3-17 months after the end of treatment; and 50% had a distant relapse. Furthermore, many previous studies reported overall response rate of 56% and a poor one year survival rate of 32% with the different chemotherapeutic regimen of bleomycin, methotrexate and lomustine (van Doorn et al., 2006; de Hullu et al., 2004; de Hullu & van der Zee, 2006). In contrast, Geisler et al. (2006) reported the very impressive outcome of cisplatin 50 mg/m$^2$ day 1 plus 5-fluorouracil 1,000 mg/m$^2$ day 1-5 using as neoadjuvant chemotherapy setting in ten patients with advanced vulvar cancer involving the anal sphincter and/or urethra. All studied patients underwent surgery except one who had a synchronous renal cell carcinoma and died prior to surgery. They demonstrated a response rate approaching 100%.

More recently, to identify the best regimen for this neoadjuvant setting, Domingues et al. (2010) analyzed three various neoadjuvant chemotherapy regimens consisting of 20 mg/m$^2$ continuous perfusion on day 1-10 of bleomycin, 100 mg/m$^2$ of paclitaxel (weekly), and 60-80 mg/m$^2$ of cisplatin on day 1 plus 750 mg/m$^2$ of 5- fluorouracil on day 1-4 utilized in locally advanced vulvar cancer in a 12-year period, to find the best regimen. The best response and overall survival rate was associated with using bleomycin. The authors hypothesized the contrary results from Geisler's report that might be from the different of the number of studied patients and dosage of chemotherapy.

To identify the real value of any regimen of neoadjuvant chemotherapy in patients with locally advanced vulvar cancer, a large multicenter, and prospective study will ultimately be required.

## 6. Vaginal cancer

The data on neoadjuvant chemotherapy in vaginal cancer is limited, due to the rarity of the disease. Benedetti Panici et al (2008) reported on eleven patients with stage II vaginal cancer who received paclitaxel 175 mg/m$^2$ and cisplatin 75 mg/m$^2$ every three weeks for three

courses followed by radical hysterectomy and vaginectomy. Three patients (27%) had a complete response and seven patients (64%) experienced a partial clinical response without serious toxicity. With a median follow-up time of 75 months, two patients (18%) had disease recurrence and one of them died of disease. The authors concluded that neoadjuvant chemotherapy followed by radical surgery is a feasible therapeutic strategy with good short and long-term results.

In recent years, case reports of two vaginal cancer patients using different neoadjuvant chemotherapy were published. The first one was presented by Takemoto et al (2009). They described a 69-year-old woman with stage III primary vaginal adenocarcinoma at recto-vaginal space. She received neoadjuvant chemotherapy consisting of paclitaxel and carboplatin following by pelvic and vaginal radiotherapy. She experienced a complete remission and remained free from recurrence one year after treatment. The other case report was released by LV et al. (2010). They presented a 41-year-old vaginal cancer patient who had a large lesion occupying the entire length of the left latero- posterior vaginal walls with left paravaginal tissue involvement. A biopsy showed a poorly differentiated squamous cell carcinoma. She was given two courses of bleomycin 15 mg/m$^2$ on day 1-2 and cisplatin 70 mg/m$^2$ on day1 every fourteen days followed by radical hysterectomy, radical vaginectomy and bilateral extraperitoneal pelvic lymphadenectomy. After the resection margins and all lymph nodes were confirmed negative by frozen section, vaginal reconstruction with bilateral pudendal thigh fasciocutaneous flaps were performed. She received four courses of bleomycin and cisplatin chemotherapy postoperatively. At 30 months, the patient was clinically free of disease and had a good sexual life.

## 7. Conclusion

In many gynecologic cancers, especially in cervical cancer and ovarian cancer, neoadjuvant chemotherapy has been explored to improve the operability and decrease the morbidity of radical surgery, without adversely affecting survival. However, research to discover the best regimen is still necessary. In some cancers such as in endometrium, vulvar and vagina, there are few publications, and further studies are required in the future.

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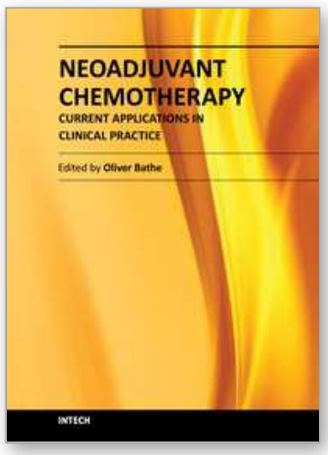


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The most significant advances in cancer therapy in recent years have involved the development of systemic therapeutics. With improvements in response rates in solid tumors, opportunities have arisen to enhance the effectiveness of surgery. Administration of systemic therapy prior to surgery - neoadjuvant chemotherapy - represents one approach by which clinicians have successfully reduced the extent of surgery and, in some instances, positively impacted on clinical outcomes. This collection of works by expert clinicians from a variety of disciplines represents an exploration of the current knowledge of the role of neoadjuvant chemotherapy in diverse tumor types.

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