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*Review*

# Neoadjuvant Chemotherapy in Locally Advanced Cervical Cancer: Review of the Literature and Perspectives of Clinical Research

ANGIOLO GADDUCCI and STEFANIA COSIO

*Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy*

**Abstract.** *Concurrent cisplatin-based chemotherapy and radiotherapy (CCRT) plus brachytherapy is standard treatment for locally advanced cervical cancer. Platinum-based neoadjuvant chemotherapy (NACT) followed by radical hysterectomy has been proposed as an alternative approach, especially for patients with stage Ib2-IIb disease. This review analyzes the most commonly used combination regimens in this clinical setting and the randomized trials comparing chemo-surgery versus definitive radiotherapy or CCRT. The combination of paclitaxel plus ifosfamide plus cisplatin (TIP regimen) obtained the highest rates of optimal pathological response, associated with elevated hematological toxicity. In a recent phase II study, a dose-dense regimen consisting of weekly paclitaxel plus carboplatin for 9 cycles has achieved optimal pathological response rates similar to those of TIP with better toxicity profile. Further studies are strongly warranted to better define the optimal regimen for the patients selected to receive NACT followed by radical surgery.*

GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries have shown 569,874 new cases of cervical cancer and 311,365 deaths due to this malignancy in 2018 (1). Concurrent cisplatin (CDDP)-based chemotherapy and radiotherapy (CCRT) plus brachytherapy represents the standard of care in patients with locally advanced disease, *i.e.* in stage FIGO 2009 Ib2-IIa2-IIb-III-IVa (2-6). A meta-analysis of 13 randomized trials showed that CCRT significantly improved 5-year overall disease-free survival (DFS) [hazard ratio (HR)=0.78, 95% confidence interval (CI)=0.70-0.87], 5-year loco-regional disease-free survival (HR=0.76, 95%CI=0.68-0.86), 5-year metastases-free survival (HR=0.81, 95%CI=0.72-0.91) and 5-year overall survival (OS) (HR=0.81, 95%CI=0.71-0.91) compared to radiotherapy alone (7). A larger survival advantage emerged for the two further trials in which adjuvant chemotherapy was administered after CCRT. An additional trial appeared to confirm the clinical benefit of this adjuvant treatment (8). In *in vitro* studies gemcitabine (GEM) was found to synergize with CDDP and have a radiosensitizing effect in six cervical cancer cell lines (9). A Mexican phase III trial randomized 515 patients with stage IIb-IVa cervical cancer to receive either CCRT (with CDDP 40 mg/m$^2$ + GEM 125 mg/m$^2$ weekly) plus brachytherapy followed by two cycles of adjuvant chemotherapy with CDDP (50 mg/m$^2$ day 1) + GEM 1000 mg/m$^2$ (days 1 and 8) every 3 weeks or the standard CCRT (with CDDP 40 mg/m$^2$ weekly) plus brachytherapy (8). The former arm experienced a trend significantly lower distant recurrence rate (8.1% *versus* 16.4%, $p$=0.005) a trend to a lower local recurrence rate (11.2% *versus* 16.4%, $p$=0.097), a significantly better progression-free survival (PFS) (HR=0.68, 95%CI=0.49-0.95) and a significantly better OS (HR=0.68, 95%CI=0.49-0.95), associated with increased, but manageable toxicity. Further investigations are needed to clarify the role of adjuvant chemotherapy after CCRT, especially in patients with positive lymph nodes, large tumor size or stage III-IVa disease (10).

Heterogeneity of cancer cells and their microenvironment influences patient response to radiotherapy, and therefore a non-invasive tool able to assess such heterogeneity, prior to or early during treatment, might deeply impact the management of individual patients, thus allowing to tailor therapy within a precision medicine paradigm (11). Radiomics is the high-throughput extraction of large amounts



*Correspondence to:* Angiolo Gadducci, MD, Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Via Roma 56, Pisa, 56127, Italy. Tel: +39 50992609, e-mail: a.gadducci@med.unipi.it

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of features from radiographic images, and the detection of radiomics features of tumor heterogeneity could offer very promising predictive and prognostic markers in several tumors, including cervical cancer (12-16).

## Neoadjuvant Chemotherapy Followed by Radiotherapy

The use of neoadjuvant chemotherapy (NACT) before radiotherapy has since long been debated. The meta-analysis of 18 randomized trials comparing NACT followed by radical radiotherapy *versus* radical radiotherapy in patients with locally advanced cervical cancer showed an OS advantage for NACT arm in trials with chemotherapy cycle lengths ≤14 days (HR=0.83, 95%CI=0.69-1.00, $p$=0.046) or CDDP dose intensities ≥25 mg/m$^2$/week (HR=0.91, 95%CI=0.78-1.05, $p$=0.20) (17). Conversely, NACT was detrimental in trials with chemotherapy cycle lengths >14 days (HR=1.25, 95%CI=1.07-1.46, $p$=0.005) or CDDP dose intensities <25 mg/m$^2$/week (HR=1.35, 95%CI=1.11-1.14, $p$=0.002). Although no study has compared CDDP- based *versus* carboplatin (CBDCA)-based chemotherapy in the neoadjuvant setting, a Japanese randomized phase III trial including 253 patients with recurrent or metastatic cervical cancer failed to evidence a difference in OS between the patients treated with paclitaxel (PTX) (135 mg/m$^2$ 24-h infusion day 1) plus CDDP (50 mg/m$^2$ day 2) and those treated with PTX (175 mg/m$^2$ 3-h infusion day 1) plus CBDCA area under curve (AUC) 5 mg/ml/min day 1) every 3 weeks (18). However, among the patients who had not received prior CDDP, OS was worse for PTX plus CBDCA arm (13.0 *versus* 23.2 months; HR=1.571; 95%CI=1.062-2.324).

In a pilot study NACT with dose-dense weekly PTX (60 mg/m$^2$) plus CBDCA (AUC2) for 6 cycles obtained a complete response in 2 and a partial response in 17 out of 28 patients with locally advanced cervical cancer, with an overall response rate of 67.8% (19). After a mean interval of 15 days (range=7-23 days), 24 patients received standard CDDP-based CCRT, 23 of these (95.8%) achieved a complete response, and 22 were still in complete response after a median follow-up of 12 months. Grade 3-4 neutropenia was the main hematological toxicity seen in 32.1% and 29.2% of patients, respectively, during NACT and CCRT.

A British single-arm phase II trial included 46 patients with FIGO stage Ib2-IVa cervical cancer scheduled to receive dose-dense weekly PTX (80 mg/m$^2$) plus CBDCA (AUC2) for six cycles followed by standard CDDP-based CCRT (20). Thirty-seven patients (80.4%) completed all six cycles of NACT, 45 (97.8%) had radiotherapy, and 36 (78.2%) received four to six cycles of CDDP during radiotherapy. A complete and a partial response were achieved in 2 (4.3%) and 30 (65.2%) patients after NACT, and, respectively, in 29 (63.0%) and 10 (21.7%) patients twelve weeks after CCRT completion. Grade 3-4 hematological and non-hematological adverse events occurred in 5 (10.9%) and 4 (8.7%) patients during NACT and, respectively, in 19 (41.3%) and 10 (21.7%) patients during CCRT. In the entire cohort, 3- and 5-year PFS rates were 68% and the 3-year and 5-year OS rates were 67%, respectively, with no deaths or progression between 3 and 5 years. These clinical outcomes were better than those of the 1243 patients treated with radiotherapy or CCRT in 42 UK centers (21). In fact, the 5-year OS of these historical controls assessed by a Royal College of Radiologists' audit was 56%. The phase II multicenter randomized trial INTERLACE (Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer, NCT01566240) is currently comparing the standard CCRT (external beam radiotherapy up to a dose of 40-50.4 Gy in 20-28 fractions concurrent with CDDP 40 mg/m$^2$/week for 5 cycles plus brachytherapy) *versus* induction chemotherapy consisting of weekly PTX (80 mg/m$^2$) plus CBDCA (AUC2) for 6 cycles followed by the same CCRT.

## Neoadjuvant Chemotherapy Followed by Radical Surgery

*Standard chemotherapy regimens*. Platinum-based NACT followed by radical hysterectomy has been proposed as an alternative approach to radiotherapy or CCRT in locally advanced cervical cancer, especially of squamous cell histology, with objective response rates ranging from 69.4% to 90.2%, pathological optimal response rates ranging from 21.3% to 48.3%, 5-year DFS rates ranging from 55.4% to 71% and 5-year OS rates ranging from 58.9% to 81%, respectively (22-32) (Table I).

The meta-analysis of 6 randomized trials including patients with early or locally advanced cervical cancer found that patients who underwent NACT plus radical hysterectomy had better PFS (HR=0.75, 95%CI=0.61-0.93, $p$=0.008) and OS (HR=0.77, 95%CI=0.62-0.96, $p$=0.02) compared to those who underwent primary radical hysterectomy, regardless of total CDDP dose, chemotherapy cycle length or tumor stage (33). NACT significantly decreased tumor size, stromal invasion depth, parametrial infiltration, lymph-vascular space involvement and nodal metastases, thus reducing the need of adjuvant radiotherapy (22, 27, 28, 33, 34).

Age >35 years (25), smaller tumor size (24, 25, 28), less advanced stage (24, 26, 28, 35), lack of nodal metastases (24, 28, 30), squamous cell histology (28), objective clinical response (28, 30), and optimal pathological response (26, 35, 36) represented favorable prognostic variables for OS of patients treated with this chemo-surgical approach. Colombo *et al*. (36) retrospectively assessed 100 advanced cervical cancer patients who received CDDP plus vincristine (VCR) plus bleomycin (BLEO) prior to radical hysterectomy. They found that the achievement of an optimal pathological response (*i.e*. a complete disappearance of tumor in the cervix

Table I. *Prognosis of patients with locally advanced cervical cancer treated with conventional neo-adjuvant chemotherapy followed by radical hysterectomy.*

| Authors | Stage | Histology | CT regimen | pts | DFS | OS |
|---|---|---|---|---|---|---|
| Sardi (22) | Ib>2 cm | SCC | CDDP + VCR + BLEO[a] | $Ib_1$ 41 | After 8 years of follow-up | OS: 82% |
| | | | | $Ib_2$ 61 | After 9 years of follow-up | OS: 80% |
| Chang (23) | Ib2-IIa2 | SCC, AD-ADS | CDDP + VCR + BLEO[b] | 68 | | 5-y: 70% |
| Benedetti (24) | Ib-III | SCC | different platinum-based regimen[c] | 210 | 5-y: 55.4% | 5-y: 58.9% |
| Huang (25) | Ib2-IIa2 | SCC, AD-ADS | CDDP + VCR + BLEO[d] | 162 | 5-y: 65% | 5-y: 69% |
| Buda (26) | Ib2-IV | SCC | CDDP +PTX+IFO[e] | 96 | 4-y: 71% | |
| | | | CDDP+IFO[f] | 108 | 4-y: 65% | |
| Katzumata (27) | Ib2-IIb | SCC | BLEO + VCR + MIT-C + CDDP[g] | 67 | 5-y: 59.9% | 5-y: 70% |
| Chen (28) | Ib2-IIb | SCC, AD, ADS | CDDP + MIT-C + 5-FU[h] | 72 | | 4-y: 71% |
| Lissoni (29) | Ib2-IVa | SCCA | CDDP + PTX + IFO[e] | 74 | 5-y: 71% | 5-y: 78% |
| | | | CDDP + PTX[i] | 80 | 5-y: 64% | 5-y: 72% |
| Angioli (30) | Ib2-IIb | SCC, AD-ADS | CDDP+PTX[l] | 115 | 5-y: 61% | 5-y: 77% |
| Shoji (31) | Ib2-IIIb | SCC | CDDP+CPT-11[m] | 42 | 5-y: 67.2% | 5-y: 68% |
| Mori (32) | Ib2-IIb>4cm | SCC | Nedaplatin+CPT-11[n] | 32 | 5-y: 78.8 | 5-y: 89.7% |

[a]CDDP 50 mg/m$^2$ d1 + VCR 1 mg/m$^2$ d1 + BLEO 25 mg/m$^2$ d1-3 q 10 for 3 cycles. [b]CDDP 50 mg/m$^2$ d1 + VCR 1 mg/m$^2$ d1 + BLEO 25 mg/m$^2$ d2-4 q for 3 cycles. [c]Minimal requirements were CDDP containing regimen with a ≥240 mg/m$^2$ total CDDP dose with a maximum of two additional drugs, administered over a period of 6 to 8 weeks. [d]CDDP 50 mg/m$^2$ d1 + VCR 1 mg/m$^2$ d1 + BLEO 25 mg/m$^2$ d1-3 q 10 for 3 cycles. [e]PTX 17 5 mg/m$^2$ d1 + IFO 5 g/m$^2$ (+ mesna 5 g/m$^2$) d1 + CDDP 75 mg/m$^2$ d2 q21 × 3 cycles. [f]IFO 5 g/m$^2$ (+mesna 5 g/m$^2$) d1 + CDDP 75 mg/m$^2$ d2 q21 × 3 cycles. [g]BLEO 7 mg d 1-5 + VCR 0.7 mg/m$^2$ d5 + MIT-C 7 mg/m$^2$ d5 +CDDP 14 mg/m$^2$ d 1-5, q21 × 2-4 cycles. [h]CDDP 100 mg/m$^2$ d1 + MIT-c 4 mg/m$^2$ d1-5 + 5-FU 24 mg/kg/d 1-5 q14 × 2 cycles. [i]PTX 175 mg/m$^2$ d1 + CDDP 75mg/m$^2$ d1 q21 × 3 cycles. [l]PTX 175 mg/m$^2$ d1 + CDDP 100 mg/m$^2$ d1 q21 × 3 cycles. [m]CDDP 70 mg/m$^2$ d1 + CPT-11 70 mg/m$^2$ d1 and 8 q21 × 2 cycles. [n]CPT-11 Irinotecan 60 mg/m$^2$ d 1 and 8 + nedaplatin 80 mg/m$^2$ d1 q21 × 2 cycles. pts, Patients; DFS, disease-free survival; OS, survival; SCC, squamous cell cervical carcinoma; CDDP, cisplatin; VCR, vincristine; Bleo, bleomicin; FU, follow-up; AD, adenocarcinoma, ADS, adenosquamous; PTX, paclitaxel, IFO, ifosfamide; MIT-C, mitomicine; CPT, irinotecan.

with negative nodes or residual disease with less than 3 mm stromal invasion) was an independent prognostic factor for OS. In the Studio Neo-Adjuvante Portio Italian Collaborative Study (SNAP01), which compared the combination of PTX plus ifosfamide (IFO) plus CDDP (TIP regimen) *versus* IFO plus CDDP (IP regimen) before radical surgery, an optimal pathological response was an independent predictor of OS with an HR of 5.88 (95%CI=2.50-13.84) (26).

A subsequent Italian multicenter retrospective study, including 333 patients with FIGO stage Ib2-IIb cervical cancer treated with different platinum-based regimens followed by radical surgery, confirmed that the pathological response to NACT was an independent prognostic variable for both PFS and OS (35). Patients who did not obtain an optimal response had a 2.757-fold higher risk of recurrence and a 5.413-fold higher risk of death than those who obtained an optimal response.

The optimal pathological response rate was 48.3% in the 89 patients of the TIP arm *versus* 23.0% in the 100 patients of the IP arm [odds ratio (OR)=3.22; 95%CI=1.69-5.88] in the SNAP01 trial, and G3-4 neutropenia, thrombocytopenia and anemia were detected in 59.1%, 14.0% and 18.3% of the former, and, respectively, in 40.6%, 7.0% and 10.9% of the latter ($p$=0.02, $p$=0.02, and $p$=0.05) (26). The optimal pathological response rate was 42.9% (95%CI=31.1%-55.2%) in the 70 patients treated with TIP *versus* 25.3% (95%CI=16.0%-36.7%) in the 75 patients treated with PTX+CDDP (TP regimen) in the SNPA02 trial (29). Therefore, TP activity was below expectation since the lower 95% confidence limit of the optimal response rate did not achieve the pre-specified minimum requirement of 22%. TIP confirmed its activity but it was associated with a significant higher incidence of grade 3-4 leukopenia, neutropenia, thrombocytopenia, and anemia than TP (53.4% *versus* 6.4%, $p$<0.0001; 76.4% *versus* 25.6%, $p$<0.0001; 23.3% *versus* 1.3%, $p$<0.0001; and 32.8% *versus* 16.7%, $p$=0.02, respectively).

The few available data about the activity of NACT followed by radical surgery in locally advanced cervical adenocarcinoma showed objective response rates ranging from 50.0% to 92.8% and optimal pathological response rates usually lower than 20% (37-45). Tabata *et al*. (41) reported a pathological optimal response in 57% of 14 patients, but the authors also included cases with microscopic residual disease <5 mm among optimal responders.

He *et al*. (46), who analyzed 2 randomized trials and 9 observational studies including a total of 1,559 patients, failed to evidence any difference in terms of either overall response rate or complete response rate to NACT between squamous and non-squamous carcinomas. Conversely, PFS and OS were better for squamous cell carcinomas. On the other hand adenocarcinoma of the uterine cervix can be classified into seven subtypes, *i.e*. endocervical (usual type), mucinous

(gastric, intestinal, signet-ring cell), villoglandular, endometrioid, clear cell, serous, and mesonephric (47), and no meaningful clinical data are available on the sensitivity of each single subtype to chemotherapy (48, 49). Kojima *et al*. (48) assessed 52 patients with FIGO stage Ib2-IIb non-squamous cervical cancer who underwent NACT with docetaxel plus CBDCA, and found that response rates (85.0% *versus* 46.2%, $p$=0.04), 5-year PFS (75.0% *versus* 38.5%, $p$=0.01) and 5-year OS (90.0% *versus* 36.9%, $p$<0.001) were better in the 20 patients with usual-type endocervical adenocarcinoma than in 13 patients with gastric-type mucinous carcinoma.

*Predictive biological variables*. Very few information is available on the biological variables predictive of response to NACT in cervical cancer. Zhang *et al*. (50) assessed the immunohistochemical expression of survivin, vascular endothelial growth factor (VEGF) and Ki-67 in 117 patients with FIGO stage $Ib_2$-$IIa_2$ squamous cell cervical cancer who received PTX (135-175 mg/m$^2$) plus CBDCA (AUC4-5) every 3 weeks for 3 cycles followed by radical hysterectomy. The efficacy of treatment, defined as complete response, partial response or stable disease, correlated negatively with Ki-67 ($p$<0.001), VEGF ($p$<0.001) and survivin expression ($p$<0.001) at univariate analysis, whereas only Ki-67 ($p$<0.001) and survivin expression ($p$=0.015) retained statistical significance at multivariate analysis.

Cervical cancer cells commonly harbor a defective $G_1$/S checkpoint owing to the interaction of high-risk human papilloma virus E6-E7 proteins with p53 and retinoblastoma protein, and therefore the activation of the $G_2$/M checkpoint could be critical for protecting neoplastic cells from chemotherapy (51). In a retrospective study, Vici *et al*. (52) assessed the levels of phosphorylated Wee1 (pWee1), a key $G_2$/M checkpoint kinase, and γ-H2AX, a marker of DNA double-strand breaks, by immunohistochemistry in 52 patients with FIGO stage Ib-IIIa cervical cancer who underwent NACT with TIP regimen followed by radical hysterectomy. Elevated levels of pWee1 and γ-H2AX significantly correlated with a lower complete pathological response rate at multivariate analysis, thus suggesting that biomarkers of DNA damage and repair may represent predictive variables of chemoresistance in cervical cancer. This is the rational for a phase I trial with the Wee1 inhibitor Adavosertib in association with external beam irradiation and CDDP in cervical, vaginal, or uterine cancer (NCT03345784).

The Hippo pathway is an emerging growth control pathway involved in organ growth control, stem cell function, regeneration, and tumor suppression (53). This pathway negatively regulates the activity of YAP and TAZ, two homologous transcriptional co-activators, that when activated, promote cell proliferation, inhibit cell death, and are involved in the carcinogenesis of several malignancies (54-58). Immunohistochemical expression of TAZ and YAP was retrospectively performed in tissue samples from 50 patients with cervical cancer who underwent NACT with TIP regimen (n.41) or CDDP-based CCRT (n.9) followed by radical hysterectomy (59). TAZ expression in cancer cells correlated with a decreased complete pathological response rate ($p$=0.041), whereas the expression of TAZ and YAP in tumor-infiltrating lymphocyte (TIL)s was associated with an increased complete pathological response rate ($p$=0.083 and $p$=0.018, respectively). Therefore, the concomitant evaluation of TAZ in tumor cells and in TILs might be a predictive factor of response to chemotherapy.

NACT in cervical cancer can induce anti-cancer immunity by altering TIL subsets (60, 61). CD8+ T cells are believed to be the front fighter against tumor, while Foxp3+ T cells can suppress the proliferation and activation of CD8+ T cells (62). Liang *et al*. (60) assessed pretreatment biopsies and radical hysterectomy specimens after two cycles of PTX (175 mg/m$^2$) plus CDDP (75 mg/m$^2$) in 137 patients with FIGO Ib2-IIa2 squamous cell cervical cancer. After NACT, Foxp3+ T cells reduced in both intratumoral ($p$<0.001) and peritumoral areas ($p$<0.001), whereas CD8+ T cell infiltration did not significantly change in both compartments. Patients who obtained a complete pathological response had post-NACT lower Foxp3+ T cells in both intratumoral ($p$=0.045) and peritumoral areas ($p$=0.014) when compared to those who did not, whereas there were no significant differences of intratumoral and peritumoral CD8+T cells between these two groups of patients. A high ratio of intratumoral CD8/peritumoral Foxp3 in residual tumors was an independent favorable prognostic variable for both PFS (HR=0.297; 95%CI=0.109-0.810) and OS (HR=0.078; 95%CI=0.010-0.598). A pilot study on 13 primary cervical tumor samples, analyzed before and after NACT, noted that the combination of PTX plus CDDP caused a significant decrease in FoxP3+ T cells with increased CD8+ T cells (61). Conversely no effect on TILs was observed after CDDP alone.

*Dose-dense chemotherapy regimens*. The search for active and well tolerated drug combinations has stimulated the assessment of dose-dense or weekly regimens, such as weekly PTX plus CBDCA, that have shown promising results with favorable toxicity profile compared with standard CDDP-based combinations in patients with recurrent or metastatic cervical cancer (63). Dose-dense weekly PTX can allow a larger percentage of cancer cells to enter the vulnerable phase of their cell cycle when cytotoxic PTX concentrations are still present, and moreover the lower PTX doses and shorter infusion times can reduce myelosuppression and other toxicities associated with standard 3-weekly schedule (64). Persistent PTX and apoptotic cells have been detected in cervical cancer tissues of patients treated with weekly schedule up to 6-7 days after the last administration (65).

Table II. *Prognosis of patients with locally advanced cervical cancer treated with dose-dense neoadjuvant chemotherapy followed by radical hysterectomy.*

| Authors | Stage | Histology | CT regimen | pts | DFS | OS |
|---|---|---|---|---|---|---|
| Mori (66) | Ib2-IIIb | SCC, AD-ADS | CBDCA + PTX[a] | 30 | 5-y: 78.6 follow-up of 17 months (range=11-30), 16/19 (84.2%) NED, 3/19 (15.8%) had recurrence and one of these (5.3%) died | 5-y: 81.8% |
| Benedetti (67) | IIa- IIIb | SCC | PTX + CDDP[b] | 22 | | |
| Tanioka (68) | Ib2-IIB | SCC, AD, ADS | PTX + CDDP[c] | 50 | 5-y PFS: 88.2% | 5-y: 88.2% |
| Gadducci (69) | Ib1-IIb | SCC, AD | CBDCA + PTX[d] | 17 | After a median interval of 12 months (3-22) from the 1st cycle of NACT, 16 (94.1%) pts: NED, 1 (5.9%) developed recurrent disease | |
| Salihi (70) | Ib1-IIb | SCC, AD-ADS | CBDCA + PTX[e] | 36 | 5-y: 61.8% | 5y: 70.8% |

[a]PTX 60mg/m$^2$ + CBDCA AUC2 q7 for 6 cycles. [b]PTX 60 mg/m$^2$ + CDDP50 mg/m$^2$ q 10 for 5 cycles. [c]CDDP 75 mg/m$^2$ d1 + PTX 80 mg/m$^2$ d 1, 8, 15 q21 for 3 cycles (2 more cycles after surgery).v [d]PTX 80 mg/m$^2$ + CBDCA AUC2 q7 for 6 cycles. [e]PTX 60 mg/m$^2$ + CBDCA AUC2.7 q7 for 6 cycles for 9 cycles. pts, Patients; DFS, disease-free survival; OS, survival; SCC, squamous cell cervical carcinoma; AD, adenocarcinoma; ADS, adenosquamous; CBDCA, carboplatin; PTX, paclitaxel; CDDP, cisplatin; FU, follow-up; PFS, progression-free survival; NACT, neoadjuvant chemotherapy; NED, no evidence of disease, AUC, area under curve.

In the last years some phase II trials have investigated the activity of dose-dense regimens before radical surgery in patients with locally advanced cervical cancer, with overall response rates ranging from 52.6% to 94%, optimal pathological response rates ranging from 17.6% to 50.0%, 5-year DFS rates ranging from 61.8% to 88.2% and 5-year OS rates ranging from 70.8%% to 88.2%, respectively (66-70) (Table II).

Mori *et al*. (66) obtained a clinical overall response in 26 of 30 patients (86.7%). A complete response was seen in 2 patients (7%), 1 of whom had a complete pathological response. A down-staging response was detected in 4 cases: 1 from IIIb to IIb, 1 from IIIa to IIb, 1 from IIb to complete clinical response and 1 from IIb to complete pathological response. The most common adverse events were hematological, and their levels were mostly acceptable. Twenty-eight patients underwent radical hysterectomy followed by adjuvant radiotherapy in 13 cases with high-risk factors. Five-year PFS and OS were 78.6% and 81.8%, respectively, in the whole series, and 79.2% and 83.1% in the patients with stage Ib2-IIb disease. These results were similar to those obtained with definitive CCRT in a series of 49 patients with stage Ib2 cervical cancer, who had a 3-year PFS of 79% and a 3-year OS of 86% (71).

In the study of Benedetti Panici *et al*. (67), 20 of 22 the patients (91.9%) completed all five planned cycles of NACT, 19 (86.4%) underwent radical surgery, and 6 of them (31.6%) received adjuvant radiotherapy or CCRT. The overall response rate was 52.6% and the optimal pathological response rate was 31.6%. Grade 3-4 leukopenia, neutropenia, thrombocytopenia and anemia developed in 4%, 14%, 0%, and 4% of cases, respectively. No treatment-related death occurred, but one (4.5%) patient had a transient ischemic attack and another one (4.5%) had a myocardial infarction. Sixteen of the 19 (84.2%) operated patients were alive with no evidence of disease after a median follow-up of 17 months.

In the study of Tomioka *et al*. (68) the overall response rates and complete pathological response rates were 94% and 28%, respectively, and grade 3-4 neutropenia and febrile neutropenia occurred in 34% and 2% of cases, respectively. Adjuvant CCRT was administered to 2 patients. It is noteworthy that a complete pathological response was found in 32.5% of 40 patients with squamous cell carcinoma *versus* 10.0% of 10 patients with non-squamous cell carcinoma, and the corresponding 5-year OS rates were 97.5% and 50%, respectively.

In our early experience, dose-dense chemotherapy obtained an overall response and optimal pathological response in 14 (82.3%) and in 3 (17.6%) of 17 patients, respectively (69). Histologically positive nodes, positive parametria and positive surgical margins were found in 12.5%, 18.7% and 6.2%, respectively, of the 16 patients who underwent radical hysterectomy. Adjuvant CCRT or radiotherapy was given to 12 patients.

Sahili *et al*. (70) administered a modified dose-dense weekly PTX/CBDCA-based chemotherapy for 9 cycles to 36 patients, of which 9 had FIGO stage Ib1 (25.0%), 7 had stage Ib2 (19.4%), 3 had stage IIa (8.3%), and 17 had stage IIb disease (47.2%). RECIST responses were observed in 32 cases (88.9%). Twenty-one patients underwent radical hysterectomy and 9 underwent conization, and histological

examination revealed an optimal pathological response in 15 (50.0%). Positive nodes, positive resection margins, and both positive nodes and resection margins were found in 16.7%, 6.7%, and 6.7%, respectively, of the cases. Grade 3-4 neutropenia, grade 3 thrombocytopenia and grade 3 anemia were detected in 56%, 3% and 11%, respectively, of patients, but there were no cases of neutropenic fever and chemotherapy-related death. Postoperative CCRT was administered to 11 patients.

### Neoadjuvant Chemotherapy Followed by Radical Surgery *Versus* Definitive Radiotherapy or Concurrent Chemoradiation

The meta-analysis of 5 randomized trials including patients with locally advanced cervical cancer showed that NACT plus radical hysterectomy achieved better overall DFS (HR=0.68, 95%CI=0.56-0.82), loco-regional disease-free survival (HR=0.68, 95%CI=0.56-0.82), metastases-free survival (HR=0.63; 95%CI=0.52-0.78) and OS (HR=0.65, 95%CI=0.53-0.80) compared to definitive radiotherapy, although with heterogeneity in both the design and results (72). In the study of Benedetti Panici *et al*. (24), NACT arm experienced a significant better 5-year PFS (59.7% *versus* 46.7%, $p$=0.02) and 5-year OS (64.7% *versus* 46.4%, $p$=0.005) compared to radiotherapy in patients with stage Ib2-IIb disease, but not in those with stage III disease (5-year PFS=41.9% *versus* 36.4%, $p$=0.29; 5-year OS=41.6% *versus* 36.7%, $p$=0.36).

Gupta *et al*. (73) randomly allocated 635 patients with FIGO stage Ib2-II squamous cell cervical cancer to receive either 3 cycles of PTX (175 mg/m$^2$) plus CBDCA (AUC5-6) every 3 weeks followed by radical surgery or standard CDDP-based CCRT. The 5-year DFS was significantly lower in the NACT arm than in CCRT arm (69.3% *versus* 76.7%; HR=1.38; 95%CI=1.02-1.87; $p$=0.038), whereas the corresponding 5-year OS rates were similar (75.4% *versus* 74.7%, HR=1.025; 95%CI=0.752-1.398; $p$=0.87). In subgroup analyses, the detrimental effect of NACT plus surgery on DFS was even greater in patients with stage IIb disease (67.2% *versus* 79.3%, HR=1.90; 95%CI=1.25-2.89; $p$=0.003), whereas no significant DFS difference was observed between the two arms in patients with stage Ib2 or IIa disease. The rates of rectal toxicity (5.7% *versus* 13.3%, $p$=0.002), bladder toxicity (2.8% *versus* 7.3%, $p$=0.017) and vaginal toxicity (19.9% *versus* 36.9%, $p$<0.001) at 90 days after treatment were significantly lower in the NACT arm, whereas 24 months after treatment there was no difference in rectal and bladder toxicities between the two groups and vaginal toxicity continued to be lower in the chemo-surgical arm (12.0% *versus* 25.6%, $p$<0.001).

A European Organization for Research and Treatment of Cancer (EORTC) trial randomized 626 patients with FIGO stage $Ib_2$-IIb cervical squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma to undergo either CDDP-based chemotherapy (with a cumulative minimum of 225 mg/m$^2$) followed by radical hysterectomy or standard CDDP-based CCRT (74). Five-year PFS was 56.9% in NACT arm and 65.6% in CCRT arm ($p$=0.021), and the corresponding 5-year OS rates were 61.8% *versus* 67.7% ($p$=0.154) (72). In subgroup analyses, the NACT arm showed a trend to better 5-year OS in patients with stage Ib2 disease (82% *versus* 76%, HR=0.89, 95%CI=0.48-1.65) and a trend to a worse 5-year OS in patients with stage IIa2 disease (69% *versus* 75%, HR=1.21, 95%CI=0.59-2.49) and those with stage IIb disease (68% *versus* 76%, HR=1.32, 95%CI=0.93-1.88). Short-term grade 3-4 adverse events occurred more frequently in NACT arm (41% *versus* 22%), whereas grade 3-4 chronic toxicities were more frequent in CCRT arm (21% *versus* 15%).

## Conclusion

According to the results of the two recent randomized clinical trials, CCRT is superior to NACT followed by radical surgery in terms of PFS in patients with stage $Ib_2$-II cervical cancer, and should represent the standard of treatment in this clinical setting. The role of NACT before CCRT or adjuvant chemotherapy after CCRT is still investigational.

According to the new 2018 FIGO staging classification for cervical cancer, stage Ib disease has been subdivided in three substages: $Ib_1$, corresponding to an invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension; $Ib_2$, corresponding to an invasive carcinoma ≥2 cm and <4 cm in greatest dimension; and stage $Ib_3$, corresponding to an invasive carcinoma ≥4 cm in greatest dimension). The involvement of regional nodes at either imaging or pathologic examination has been described as stage IIIc (stage $III_{c1}$, pelvic node metastasis only; stage $III_{c2}$, para-aortic node metastasis with or without pelvic node involvement) (75).

Disruption of the cervical stromal ring on magnetic resonance imaging (MRI) is strongly predictive of microscopic parametrial infiltration in patients with early invasive cervical cancer (76, 77). The patients with this MRI finding, if submitted to primary surgery, usually receive adjuvant radiotherapy or CCRT. Based on the 2018 FIGO classification, patients with stage $Ib_1$ disease or with stage $Ib_2$-$IIa_1$ disease with intact stromal ring should undergo primary radical surgery and those with $Ib_2$-$IIa_1$ disease with disrupted stromal ring or with $Ib_3$ disease could undergo either definitive CCRT or NACT followed by radical surgery. These latter treatments should be indicated especially in relatively young women, also for the lower incidence of long-term vaginal toxicity and compromise of sexual life. Patients with stage ≥$IIa_2$ disease should undergo definitive CCRT.

Clinical trials assessing NACT followed by surgery in cervical cancer have shown that TIP regimen has obtained the highest rates of optimal pathological response, associated with an elevated incidence of grade 3-4 neutropenia, thrombocytopenia and anemia (26, 29). The dose-dense weekly PTX/CBCDA-based regimen proposed by Salihi *et al*. (70) appeared to achieve optimal pathological response rates similar to those of TIP regimen with a better hematological toxicity profile. These very promising results compared with those obtained with other dose-dense or weekly regimens could be due to both the inclusion of a 25% of patients with old FIGO stage 1b1 disease and the administration of a higher number of weekly chemotherapy cycles before surgery (nine *versus* six). Further studies on larger series of well characterized patients are strongly warranted to better define the optimal regimen for patients with 2018 FIGO stage $Ib_2$-$IIa_1$ cervical cancer with disrupted stromal ring or with stage $Ib_3$ cervical cancer selected to receive NACT followed by radical surgery.

## Conflicts of Interest

The Authors declare no conflicts of interest.

## Authors' Contributions

Conceptualization, Writing - original draft: Angiolo Gadducci; Data curation, formal analysis, methodology, writing, review and editing: Angiolo Gadducci and Stefania Cosio.

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