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Reference:

Van Dam Peter André, Rolfo Christian, Ruiz Rossna.- Neoadjuvant trials can accelerate research on novel systemic treatment modalities in cancer of the uterine cervix
European journal of surgical oncology - ISSN 0748-7983 - Oxford, Elsevier sci ltd, 43:12(2017), p. 2245-2247
Full text (Publisher's DOI): <https://doi.org/10.1016/J.EJSO.2017.09.018>
To cite this reference: <http://hdl.handle.net/10067/1485510151162165141>

Accepted Manuscript

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PII: S0748-7983(17)30708-4

DOI: [10.1016/j.ejso.2017.09.018](https://doi.org/10.1016/j.ejso.2017.09.018)

Reference: YEJSO 4755

To appear in: *European Journal of Surgical Oncology*

Received Date: 30 August 2017

Accepted Date: 1 September 2017

Please cite this article as: van Dam P, Rolfo C, Ruiz R, Neoadjuvant trials can accelerate research on novel systemic treatment modalities in cancer of the uterine cervix, *European Journal of Surgical Oncology* (2017), doi: 10.1016/j.ejso.2017.09.018.

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Neoadjuvant trials can accelerate research on novel systemic treatment modalities in cancer of the uterine cervix

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Cancer of the uterine cervix (CC) reflects disparities in access to healthcare across the world; although being highly preventable, this disease is still a major public health problem in less developed regions. Globally it is the second most prevalent cancer in women, most cases being diagnosed at an advanced stage.¹ Inoperable CC will continue to be highly prevalent during the next decades as screening programs and vaccination campaigns are still unavailable in most countries and are not entirely effective. Currently, locally advanced disease is treated with (chemo)radiotherapy and metastatic disease with platinum-based chemotherapy (+/- bevacizumab). First- and second-line systemic treatments are not very effective, and early clinical trials with targeted therapy have not yet identified new targeted drugs with superior response rates.²

The role of neoadjuvant chemotherapy (NACT) has been investigated during the past 3 decades in an attempt to improve the prognosis of patients with locally advanced cervical cancer. It was first reported in 1988 by Benedetti-Panici et al who used combination chemotherapy (cisplatin, bleomycin +/- methotrexate) to treat patients with FIGO stage IB2–III cervical cancer.³ A response rate of 83% was observed, 15% of these being pathological complete responses. Responding patients underwent laparotomy, but 8% were not amenable for radical surgery. The 10-year survival estimates were 91%, 80% and 34.5% for FIGO stage IB2–IIA bulky, IIB and III, respectively. Two recent meta-analyses showed that overall survival (PS) and progression-free survival (PFS) were significantly improved with

NACT followed by surgery compared with surgery alone (23% reduction in the risk of death).^{4,5} The platinum/paclitaxel combination is now the preferred regimen in the neoadjuvant setting, and preliminary data indicate that dose-dense regimens are feasible and effective with an overall response rate of 68–87%. A weekly regimen with carboplatin/paclitaxel before chemoradiation seems to be promising. The INTERLACE ongoing trial will help to confirm whether additional short-course chemotherapy given weekly before chemoradiation will lead to an improvement in overall survival. He et al assessed the efficacy of NACT in different histological types of cervical cancer in another meta-analysis.⁶ Squamous carcinoma of the cervix (SCC) was associated with a higher short-term response rate than non-SCC in randomized controlled trials (HR = 6.57, 95%CI = 1.72–25.12) for complete and partial responses. For the long-term outcome of NACT, patients with SCC experienced a significantly higher 5-year OS and PFS when compared to patients with non-SCC in pooled (HR = 1.47, 95%CI = 1.06–2.06) and observational studies (HR = 1.96, 95%CI = 1.61–2.38, $P > 0.05$) other than randomized controlled trials. Moreover, this difference was especially obvious when the subgroup analysis was restricted to patients in stages above IIB (HR = 2.06, 95%CI = 1.79–2.36) rather than in stages IB –IIB (HR = 1.33, 95%CI = 0.99–1.79). Tierney et al compared NACT plus surgery with radiotherapy in a meta-analysis including data from five trials and 872 patients.⁵ The combined results from all trials indicate that NACT results in a reduction in the risk of death by 35% (HR = 0.65, 95% CI = 0.53–0.80, $P = 0.0004$) and in improved 5-year survival rate by 14% only if the period of cisplatin chemotherapy was shorter than 14 days or weekly doses of cisplatin were >25 mg/m². NACT followed by radiotherapy may be detrimental with a low dose of cisplatin and longer cycle intervals. Limited data are available comparing NACT followed by surgery versus primary chemoradiotherapy in women with advanced locoregional CC. Two ongoing phase III trials will hopefully clarify this issue in the near future (EORTC 55994 and a study sponsored by the Department of Atomic Energy of India).

NACT has also been used to make fertility-sparing surgery feasible in women with cervical lesions >2 cm.⁷ Only a few centers perform these procedures, and thus such an approach remains largely in the experimental stage. Current data are not sufficient to identify the optimal surgical procedure after NACT: a simple cone biopsy, a simple trachelectomy or a

radical trachelectomy. The high rate of pathological responses confirms the effectiveness of the preoperative treatment for reducing the tumor volume, allowing the removal of only a cervical cone instead of the entire cervix with cardinal ligaments as needed by radical trachelectomy. Successful pregnancies are possible after such integration. Although no randomized trials are available, the rate of fertility preservation and obstetrical outcome seems superior after neoadjuvant chemotherapy compared to primary radical trachelectomy.

Response to NACT is a good surrogate endpoint of survival in patients with locally advanced cervical cancer. Liang et al performed a detailed histopathological study using a novel pathological grading system in 190 patients with bulky stage IB2 or IIA cervical squamous-cell cancer who underwent neoadjuvant chemotherapy followed by surgery.⁸ Multivariate analyses showed that the pathological response grading system was the only independent predictor for PFS and OS ($P = 0.001$ and $P = 0.007$). Pre-NACT cell cycle phase-specific markers do not appear to predict disease grade, stage, or outcome in patients with cervical cancer.⁹ This is not surprising given that most cervical cancers display an aggressive, so-called actively cycling phenotype which may reflect the viral etiology underlying the disease. However, post-NACT proliferation markers are of prognostic value.⁹ Ki67 has proved to be a significant predictor of overall survival in multivariate analysis. Other useful biomarkers for response to NACT are proliferating cell nuclear antigen (PCNA), the apoptotic index, MDR1 expression, aldehyde dehydrogenase 1 (ALDH1) and sirtuin expression. Dynamic contrast-material-enhanced magnetic resonance imaging parameters, especially the time-signal intensity curve, and diffusion-weighted imaging (DWI) are associated with complete response and incomplete response, and could potentially help oncologists with management decisions.¹⁰ Fu et al investigated the changes to DWI correlated with histopathology after NACT in patients with locally advanced cervical cancer (LACC). The apparent diffusion coefficient value of the group with partial or complete response after the first chemotherapy was higher than that before chemotherapy ($P = 0.002$), and expressions of three pathological indicators – tumor cell density, PCNA, and aquaporin 1 (AQP1) – significantly decreased after the first NACT compared with those prechemotherapy ($P <$

0.001). Changes of PCNA expression were negatively correlated with changes in ADC values after the first NACT in the patients with complete and partial responses ($r = -0.56$, $P = 0.03$).

Up to now the scientific society and pharmaceutical industry have shown little interest in developing new (targeted) treatment modalities to improve the outcome of patients with advanced and recurrent CC. In fact CC is often not included in phase I–II basket trials assessing experimental drugs. Traditionally, testing novel systemic treatments in advanced CC requires large and expensive randomized clinical trials involving hundreds of patients, with follow-up extending over several years before results emerge. Neoadjuvant experimental therapy (NET) provides a unique opportunity for faster and cheaper studies assessing the responsiveness to targeted drugs and/or immunotherapy. CC is easily and safely accessible for repeated tumor biopsies, allowing intra-patient comparisons. NET can be performed in a concept of proof setting as short treatment courses (2–4 weeks) before standard treatment, using biomarkers as endpoints. It can also be tested with randomized trials comparing standard chemotherapy versus a combination of experimental treatment using operability and/or pathological response as endpoints, jointly with biomarkers for response, thereby gaining insight into molecular changes associated with tumor response. While immunotherapy is emerging as a potential treatment modality of CC, NET may offer a unique opportunity to assess the immune response in vivo. Patients with recurrent metastatic disease are often immunocompromised, and it is therefore important to assess immunotherapy in earlier stage patients. We therefore advocate the use of NET as a tool to accelerate translational and clinical research into better treatment of CC. Performing this research in parts of the world with a high incidence of the disease is mandatory to achieve this goal. Such an approach is ethically defensible only if strategies are developed to reduce costs and to access new active drugs in these countries.

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Conflicts of interest

The authors have no conflicts of interest

Funding

This study was not funded.

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